PREVENTION AND REVERSAL OF CHRONIC DISEASE: LESSONS LEARNED

By

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ABSTRACT

For a decade, our research group has been developing protocols to prevent and reverse chronic diseases. The present monograph outlines the lessons we have learned from both conducting the studies and identifying common patterns in the results. The main product of our studies is a five-step treatment protocol to reverse any chronic disease, based on the following systemic medical principle: ***at the present time, removal of cause is a necessary, but not necessarily sufficient, condition for restorative treatment to be effective***. Implementation of the five-step treatment protocol is as follows:

FIVE-STEP TREATMENT PROTOCOL TO REVERSE ANY CHRONIC DISEASE

Step 1: Obtain a detailed medical and habit/exposure history from the patient.

Step 2: Administer written and clinical performance and behavioral tests to assess the severity of symptoms and performance measures.

Step 3: Administer laboratory tests (blood, urine, imaging, etc)

Step 4: Eliminate ongoing contributing factors to the chronic disease

Step 5: Implement treatments for the chronic disease

This individually-tailored chronic disease treatment protocol can be ***implemented with the data available in the biomedical literature now***. It is general and applicable to any chronic disease that has an associated substantial research literature (with the possible exceptions of individuals with strong genetic predispositions to the disease in question or who have suffered irreversible damage from the disease). To prevent any chronic disease, eliminate those contributing factors that serve as a basis for Step 4.

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This monograph is not intended as a substitute for the medical advice of physicians. The reader should regularly consult a physician in matters relating to his/her health and particularly with respect to any symptoms that may require diagnosis or medical attention. Any information in the monograph that the reader chooses to implement should be done under the strict guidance and supervision of a licensed health care practitioner.

PREFACE

Why did I write this monograph, what are its contents, what is new, who is the intended audience, and how will readers benefit from it?

Motivation

Non-communicable diseases have overtaken communicable diseases as the leading cause of global mortality. The impacts of non-communicable disease expansion on healthcare and associated costs have been dramatic. In the USA, these costs, and how to deal with them, have become a central political issue.

The mainstream medical approach emphasizes treatments over prevention for non-communicable diseases. Given the expansion of non-communicable diseases, the present treatment-dominant approach is insufficient. Greater balance between treatment and prevention is required. Eliminating the actionable foundational causes of these diseases is at least as important as applying new treatments, if there is to be any hope for full or partial reversal of non-communicable diseases, as well as prevention.

Toward that end, I developed a systemic medical principle that would form the bedrock of a healing protocol for diseases: ***at the present time, removal of cause is a necessary, but not necessarily sufficient, condition for restorative treatment to be effective*** (where "removal" encompasses "neutralization" in those cases where actual "removal" is not possible, and "restoration" encompasses restoration of *health* to the organ/tissue as well as restoration of *function*). To prevent diseases, the actionable foundational causes shown by the biomedical literature to potentially contribute to the diseases need to be removed as comprehensively, thoroughly, and rapidly as possible. To reverse diseases (if irreversible damage has not been done and genetic predisposition to the disease in question is not a dominant factor), the preventive steps above need to be implemented as well. If the preventive protocols alone are inadequate for reversing disease progression, they need to be augmented by treatments. The first step in either disease prevention or reversal is to identify the full spectrum of potential foundational causes/contributing factors for the disease(s) of interest.

Based on our studies of three chronic diseases, we have found:

1) much of the information required to identify and eliminate these foundational causes of disease is in the biomedical literature already, but is not being extracted and exploited adequately;

2) the biomedical literatures for many chronic diseases are large, and extracting these foundational causes comprehensively from the literatures is a complex text mining problem;

3) the same holds true for treatments and biomarkers.

Contents

The overall theme of the present monograph is preventing and reversing chronic disease based on the systemic medical principle described above. The specific focus of the present monograph is 1) summarizing the methodologies used in our chronic disease studies to prevent and reverse these diseases, and 2) summarizing the lessons learned and patterns identified from these studies.

There are lengthy appendices in the present monograph describing the text mining/information technology advances that allowed 1) the existing and potential chronic disease treatments and contributing factors to be extracted efficiently from the large numbers of journal articles retrieved from the premier biomedical literature, and 2) the impacts of these treatments and contributing factors to be extracted from the literature. Major advances were made in the text mining approach for extracting both existing and potential treatments and contributing factors from the biomedical literature (and their impacts).

Novelty

While the individual existing and potential chronic disease contributing factors and treatments identified in this monograph are "known", in the sense that they exist scattered throughout the published literature (although the potential chronic disease contributing factors and treatments have not been previously associated with the chronic disease in the literature), they have not been integrated to the extent they are integrated in this monograph. The new "insights" in this monograph are:

1) the sheer number of existing and potential chronic disease contributing factors, biomarkers, and treatments;

2) the sheer number of potential *combinations* of chronic disease contributing factors and treatments that have to be identified and researched (many of whose individual components have not yet been identified);

3) the sheer number of chronic disease biomarkers and symptoms that can be used as diagnostics to identify causes and treatments for individual patients;

4) the approach for discovering treatments from the non-chronic disease literature, which allows both the *re-purposing of drugs* that have been used for treating other diseases and identification of non-drug substances that will correct the abnormal chronic disease biomarker values;

5) the chronic disease treatment protocol that can be tailored to any individual patient.

Audience

There are three communities to whom this monograph is targeted. First is the "chronic disease prevention and reversal" community. This encompasses the public health community, the chronic disease research community, medical practitioners involved clinically with chronic disease prevention and reversal, caretakers for chronic disease patients, and individuals interested in what the present approach has to offer (they should heed the warnings in the Disclaimer).

Second is the text mining and information technology community. This would cover the full spectrum of researchers interested in extraction of useful information from any type of text, since the techniques developed in this monograph can be readily adapted to extracting useful information from myriad types of biomedical and non-biomedical text.

Third is the broader medical and health policy community. The ***methodology is applicable to prevention and reversal of any disease*** that has an associated substantial research literature.

Benefits

The interested reader of this monograph will gain a deeper understanding of the main contributing factors to, and treatments available for, the three chronic diseases studied. The reader will also gain an understanding of the broad spectrum of rigorous actions required to prevent and/or reverse chronic disease. Finally, and most importantly, the motivated reader will see that much of what is required to prevent and reverse chronic disease ***may be available in the here and now*** (for those who have not suffered irreversible damage or have an overwhelming genetic predisposition for the chronic disease of interest)!

Ronald N. Kostoff, 10 November 2019, Gainesville, VA

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1. INTRODUCTION

1A. Concept for Preventing and Reversing Chronic Diseases

Non-communicable diseases have become the leading cause of death globally. They lead to 4-fold greater mortality than communicable diseases [WHO, 2016]. While the per capita mortality rate for infectious diseases has declined precipitously over the past century, the per capita mortality rate for non-communicable diseases has remained roughly constant [Hansen et al, 2016].

Whether this constant per capita mortality trend for non-communicable diseases will continue into the future is highly questionable. The chronic diseases we studied have a strong environmental component. There have been many potentially harmful and effectively un-regulated high-technology additions to the environment in the past few decades (e.g., non-ionizing radiation (from cell phones, Wifi), vaccine combinations, agricultural chemicals, etc., have expanded greatly). Because of latency delays, it is difficult to link the disease and potentially harmful environmental factors that may have occurred decades earlier. As, for example, our Alzheimer's Disease (AD) study showed [Kostoff et al, 2018], the adverse impact of recent potentially harmful environmental and dietary additions on AD biomarkers and symptoms ominously portends increased incidence and prevalence of AD in the future. This holds true for all three chronic diseases we studied.

Many of the toxic stimuli that are contributing factors to AD also contribute to myriad other serious diseases [Kostoff, 2015]. Many of these diseases can be fatal, and may not have the multi-decadal latencies associated with AD. Thus, these lethal diseases serve to cull out people who would have been high-risk candidates for AD had they lived. This culling out of high-risk individuals artificially depresses and masks the real incidence of AD had these high-risk people survived. This line of reasoning is applicable to the other chronic diseases we studied.

It was important to understand better what was driving the disparity in mortality trends between communicable and non-communicable diseases, and to ascertain whether the text mining approaches I had developed for discovering new treatments for disease could help reverse the trend. About a decade ago, I undertook a two-pronged approach to examine the biomedical literature addressing non-communicable diseases. The first prong consisted of identifying the contributing factors to the non-communicable diseases, and the second prong was to develop treatment protocols for preventing and reversing these chronic diseases.

The first prong was motivated by a TEDx talk given by Dr. Terri Wahls about a decade ago [Wahls, 2011]. She was on the faculty of the University of Iowa Medical School when she developed Multiple Sclerosis (MS). As time progressed, she became non-ambulatory, teaching and performing other duties in a wheelchair. Finding no relief from the mainstream medical approaches to MS, she researched the causes and potential treatments for MS herself. Based on her research, she hypothesized that poor diet may have been the driving factor behind her downward progression of MS, and substitution of a good diet might reverse the disease. She also hypothesized that a technique called Neuromuscular Electrical Stimulation (NMES), which had only been used previously for treating athletic injuries, could help reverse the nerve damage caused by the MS.

She improved her diet to a higher level, then tried the NMES. No improvement. She improved her diet to the next higher level, and tried the NMES again. Still no improvement. When she further improved her diet, the MS began to reverse and NMES began to reverse the nerve damage. As of a few years ago, she was riding horses, hiking, and doing other strenuous activities.

Her story changed my thinking about disease, and what is necessary to prevent and reverse disease. Treatments were insufficient as long as the factors that contributed to the disease were still operable. As a result, I developed a systemic medical principle that, in its latest incarnation, states: ***at the present time, removal of cause is a necessary, but not necessarily sufficient, condition for restorative treatment to be effective***. The principle has two caveats: irreversible damage has not been done, and there is not an overwhelming genetic predisposition to the disease in question. However, in most cases, we will not know whether irreversible damage has been done or whether there is an effective genetic predisposition to the disease until essentially all the important contributing factors have been eliminated. This principle is general, and applicable to prevention and reversal of ***any*** disease. The methodology that has been developed based on this principle is general, and applicable to any disease as well.

To prevent any disease, the foundational causes shown by the literature to underlie the disease symptoms and biomarkers need to be identified and removed as comprehensively, thoroughly, and rapidly as possible. To reverse any disease (given the above caveats), the preventive steps above need to be implemented, and treatments to reverse the disease progression need to be applied.

The efficacy of the methodology for preventing and reversing any disease depends on how thoroughly the foundational causes, treatments, biomarkers, and symptoms of the disease of interest have been identified. As will be shown in this monograph, a wide spectrum of existing foundational contributing factors has been identified for the chronic diseases we have studied, and a wide spectrum of existing treatments and symptoms and biomarkers has been identified as well. Combining these results allows development of a treatment protocol that can be tailored to individual patients and applied to any chronic disease. Most importantly, this treatment protocol (based on the systemic medical principal described above) is ***available with the information at our disposal today!***

1A1. Concept Feasibility

Currently, the protocol we have developed is a concept. What evidence exists to demonstrate its feasibility? I will provide an example from AD, but it can be extrapolated to the other chronic diseases as well. In 2017, two books were published on reversing early stage AD [Bredesen, 2017; Sherzai and Sherzai, 2017]. All the authors were credible neurologists, with long-standing experience in treating neurodegenerative diseases.

One of the authors is Dale Bredesen. He is an AD researcher/clinician who has shown that "reversal of cognitive decline in patients with early Alzheimer's disease or its precursors, MCI (mild cognitive impairment) and SCI (subjective cognitive impairment)" is obtainable today [Bredesen, 2014]. Basing his approach on optimizing metabolic parameters, Bredesen used a combination of eliminating some potential AD contributing factors, substituting positive health practices, and adding dietary supplements to achieve his AD/MCI/SCI reversal results.

Sherzai and Sherzai are AD researchers/clinicians who claim to have had very positive results with patients based on: "lifestyle intervention as the cure for cognitive decline" [Sherzai and Sherzai, 2017]. Their lifestyle modification approach (based on addressing their assumed four main pathways to AD: inflammation, oxidation, glucose dysregulation, lipid dysregulation) has five main components: nutrition, exercise, stress management, adequate sleep, and mental challenges.

Bredesen's and the Sherzais' approaches can be viewed as one "footprint" of the more general systemic medical principle for preventing or reversing disease described in the current monograph. Our approach is not constrained by hypotheses based primarily on symptoms/pathological mechanisms. We use symptoms, pathological mechanisms, and other abnormal AD characteristics as a guidepost to identify causes to be eliminated and treatments to be implemented for individual patients. Our approach is based on cause and effect as evidenced in the premier biomedical literature. We identify as many AD biomarkers and symptoms as exist in the literature, and then relate adverse changes in the values of these AD biomarkers and symptoms to potential underlying foundational causes. Preferably, the research findings will identify the biological mechanisms that link a foundational cause to its impact(s) on AD biomarkers and symptoms. However, even in the absence of identifying such mechanisms, the linkage is retained. We also relate beneficial changes in the values of these AD biomarkers and symptoms to potential treatments, again, whether or not the biological mechanisms that link treatments to positive impacts have been identified.

Since our approach incorporates the positive aspects of the Bredesen and Sherzai approaches, but is far more extensive, we would expect (with some degree of confidence) the results from our approach to be at least as beneficial as those from Bredesen and the Sherzais, and possibly be effective into the higher stages of AD as well.

1A2. Concept Cost Impacts

There are two major benefits that would result from wide-scale implementation of our concept: improved health and longevity, and greatly reduced healthcare costs. I will address the latter in this section.

There are many schemes being proposed in the USA today to reduce the massive level of healthcare costs. They go by the names of Medicare for All, single-payer, public option, universal health care, etc. Essentially all these proposals are book-keeping schemes. They do little to reduce the people, infrastructure, and procedures involved in healthcare. Rather, they play games with who is going to pay the bills, and which scheme will have the greatest political impact. They are akin to re-arranging the deck chairs on the Titanic!

None of these schemes will do very much to reduce total healthcare costs. We will still need myriad specialists, myriad support personnel, myriad diagnostics, myriad drugs, myriad therapies, myriad nursing homes, etc, under the mainstream medical approach used today. Paperwork may be reduced, and some savings may result from eliminating the insurance companies, but the bulk of healthcare costs will remain. In fact, bringing in more people to healthcare system coverage under these proposals will result in increased total costs, unless drastic changes in healthcare procedures are adopted.

The only way to reduce healthcare costs substantially is to keep people out of the medical system in the first place, wherever possible. Procedures need to be implemented that will minimize peoples' interactions with the medical system. Rather than play accounting games to reduce healthcare costs a few percent, eliminate as broadly as possible those exposures and substances that are known to contribute to disease.

As the remainder of this monograph will show, we already know most of the factors that contribute to non-communicable diseases. For the chronic diseases we have studied over the past decade, there are hundreds of contributing factors for each disease, most of which are not addressed under existing medical care. Additionally, in some recent toxicology studies I have performed to support the protocols, I have found there are orders of magnitude differences between exposure limits set by Federal regulators and exposures shown to cause damage in the biomedical literature [Kostoff, 2018].

Significant reduction of healthcare costs requires two major steps. First, the medical profession needs to place far more emphasis on reducing contributing factors to disease in their treatment protocols, along the lines suggested in this monograph. This also requires educating patients on the importance of this approach for their healing. This step alone would greatly reduce peoples' interactions with the medical system.

Second, government at all levels needs to bring the regulated exposure limits in line with the findings in the medical literature. This includes limits on chemical exposures, radiation exposures (especially non-ionizing radiation), biotoxin exposures, etc, taking into account potentially synergistic effects due to combinations of myriad toxic stimuli exposures. Implementation of the above two steps would lead to far more health improvement and cost reductions than any of the accounting schemes under present consideration.

1B. Implementation

My previous work on using text mining to treat diseases had focused almost exclusively on discovering new treatments for diseases using Literature-Related Discovery, an off-shoot of Literature-Based Discovery I had developed about a decade ago [Kostoff RN, 2008, 2011; Kostoff and Briggs, 2008; Kostoff and Los, 2013; Kostoff, Block, Stumpf et al, 2008; Kostoff, Briggs, and Lyons, 2008]. I then began to expand my text mining approach to identifying contributing factors as well as treatments. I would identify not only potential new contributing factors and treatments for the disease of interest, but would also include identifying known contributing factors and treatments for the disease of interest.

The initial chronic disease I examined was chronic kidney disease (CKD) [Kostoff and Patel, 2014], the selection of which was requested by a colleague who had been recently diagnosed with Stage III CKD. I developed more powerful LRD techniques to identify potential new treatments, and was able to apply these techniques to identify potential new contributing factors. Equally important, as it turned out, I developed new text mining approaches to identify comprehensively the known treatments and contributing factors for CKD. In Appendix 1, I outline the text mining approaches used for the CKD study. The detailed text mining approaches for each of the chronic diseases I studied are presented in later appendices.

The results from the CKD study were very surprising because of their magnitude and breadth. About 800+ contributing factors, about 800+ treatments, and almost 400 biomarkers/symptoms were identified from the existing CKD literature. I believe many more of each were possible, especially those appearing infrequently in the CVD literature. In addition, almost 100 new contributing factors and almost 100 new treatments were identified as discovery from the non-CKD literature. Again, much more discovery was possible, since only very simple queries were used, and the analysis of what was retrieved was arbitrarily terminated.

My next published study didn't focus on a specific disease. After the CKD study, it became clear to me that a much more comprehensive understanding of the broader impacts of potentially toxic substances on all diseases simultaneously was required before moving ahead to develop protocols to prevent and reverse other diseases. I conceived of an approach that would identify 'all' contributing factors to 'all' diseases. This methodology is presented in Appendix 2. The comprehensive study was a massive effort that was limited severely by my computer system capabilities and my time resources. The final product was an eBook entitled "Pervasive Causes of Disease" [Kostoff, 2015]. It identified about 8,000 causes spread over about 4,000 diseases. About 800 of the causes were deemed 'pervasive', meaning they impacted at least an arbitrarily-selected threshold number of diseases. The relationships tended to be many-to-one and one-to-many. One cause could impact many diseases, and many causes could impact one disease.

The cause-disease matrix was very sparse; only a relatively few of the 32,000,000 cells in the matrix had values. Far more cause-disease linkages should be expected. The various biological systems are interconnected (neural, immune, endocrine, circulatory, etc), and an adverse impact of a substance on one of these systems would be expected to have a ripple effect on the other intersecting systems. A more comprehensive and adequately-resourced study could have uncovered many more cause-disease relationships from the existing literature. Additionally, even if all the cause-disease relationships had been identified from the existing biomedical literature, the matrix still may have been relatively sparse. In order for a cell to have an entry, the underlying research would have had to be funded, the research conducted, and the research published. In Chapter 9 of the Pervasive Causes of Disease eBook, I discuss reasons why some of this research never sees the light of day, especially for topics that have commercial/political/military sensitivity. Also, in the design and conduct of the research, the researchers don't include the thousands of biomarkers that would cover all these diseases in any one experiment or study. They usually measure a handful of such biomarkers in any one study, selected mainly because of mechanism assumptions, and their findings are typically limited to one or a few diseases.

Our next published study focused on Alzheimer's Disease (AD) [Kostoff, Porter, and Buchtel, 2018]. Based on lessons learned from the CKD study and the Pervasive Causes of Disease study, we developed a more streamlined approach, and were more selective in the number of different text mining approaches used to identify contributing factors, treatments, and symptoms/biomarkers. This streamlined methodology is shown in Appendix 3. We also developed a more formal treatment protocol for preventing and reversing AD. As in the CKD study, we found many hundreds of contributing factors, treatments, and biomarkers/symptoms, and could have identified many more of each by using additional approaches.

In the AD biomedical literature, there are at least 20+ hypotheses (e.g., amyloid hypothesis, tau hypothesis, etc). We assumed all had some validity, and selected three or four biomarkers and symptoms to represent each hypothesis in the diagnostic steps of the protocol. All the AD hypotheses identified were centered around AD pathology, specifically, general biomarker abnormalities and symptoms (e.g., amyloid plaques, tau hyperphosphorylation, oxidative stress, inflammation, etc) associated with AD. The typically high-technology treatments that accompany these hypotheses focus on removing/suppressing these pathological symptoms, rather than removing the causes of these symptoms. These treatments (in the absence of comprehensive cause removal) are not efficacious because they violate the systemic medical principle that forms the basis of our methodology.

Interestingly, there are no foundational causes-based hypotheses of AD, e.g., the Deficient-Diet Hypothesis, the Iatrogenic Hypothesis, the Sedentary Lifestyle Hypothesis, the Radiation Exposure Hypothesis, the Toxic Chemical Exposure Hypothesis, etc. There are many articles in the literature 1) questioning the validity of each of the above-listed pathology-based AD hypotheses and 2) showing the deficiencies in their associated treatments for reversing AD.

The strategy of identifying symptoms as pathological mechanisms that must be suppressed or removed for healing is a mainstay of Western Medicine. However, another perspective is to view these symptoms as having two basic functions: serve as a warning signal that dysfunction exists and actions need to be taken to remove the cause of this dysfunction, and serve as a protective mechanism.

There are many examples in the biomedical literature supporting the concept of disease symptoms as warning signals and protective mechanisms, as shown by the following:

EXAMPLES OF DISEASE SYMPTOMS AS PROTECTIVE MECHANISMS

- "the down-regulation of energy metabolism in AD is a protective response of the neurons to the reduced level of nutrient and oxygen supply in the microenvironment" [Sun, Feng, Liang et al, 2012].
- "Neurofibrillary tangle formation as a protective response to oxidative stress in Alzheimer's Disease" [Nunomura, Takeda, Moreira et al, 2009];
- "Autophagy is a protective response to the oxidative damage to endplate chondrocytes in intervertebral disc" [Chen, Lv, Li et al, 2017];
- "loss of appetite in the acute phase of illness is indeed an adaptive, protective response that improves cell recycling (autophagy) and detoxification" [Schutz, Bally, Stanga et al, 2014];
- "Cataract is a self-defence reaction to protect the retina from oxidative damage" [Wegner and Khoramnia, 2011].

Additionally, in his 2017 book [Bredesen, 2017], Bredesen states: "Alzheimer's disease is actually a protective response to, specifically, three different processes: inflammation, suboptimal levels of nutrients and other synapse-supporting molecules, and toxic exposures." Other AD researchers have drawn similar conclusions. If Bredesen's view that the AD symptoms serve as a protective response against more serious damage is correct, then the mainline drug-based AD treatment approach of

suppressing these symptoms without removing the foundational causes that underlie these symptoms comprehensively in parallel

1) effectively removes the protective shield offered by these symptoms and thereby

2) exacerbates the progression of AD!

Our most recent study focused on Peripheral Neuropathy (PN)/Peripheral Arterial Disease (PAD) [Kostoff, 2019]. We improved our techniques for identifying existing contributing factors, treatments, and biomarkers/symptoms. As a result, we identified 800+ contributing factors, 1,000+ treatments, and 1000+ biomarkers and symptoms. The PN/PAD methodology is contained in Appendix 4. Again, identifying far more items was possible with a well-funded study.

A note about the very large number of existing treatments identified in all three chronic disease and prevention studies. In all three, the treatments identified covered research over the past ~two-three decades. Treatments that have 'failed' in human clinical trials are not excluded. The reason for retaining these 'failed' treatments is as follows:

My reading of thousands of abstracts on laboratory experiments and clinical trials of potential chronic disease treatments has shown

1) in vitro experiments typically performed on cells tend to have reasonably positive outcomes, at least for those papers that surface in the peer-reviewed published literature;

2) in vivo experiments typically performed on rodents (but other small animals as well) tend to also have reasonably positive outcomes, albeit somewhat less than in vitro experiments;

3) when these potential treatments reach the human clinical trial stage, especially the later phases, the success rates plummet!

The explanation for this discrepancy given most often is the species difference. Humans are different from rodents et al, and their physiological responses to stimuli are different as well. However, the toxic experiential and exposure background differences between humans who live in the real-world sea of myriad toxic exposures and animals who live in the very controlled environment of the laboratory are rarely, if ever, discussed.

For the three chronic diseases studied, there were many hundreds of potential contributing factors identified (ranging from Lifestyle to Occupational/Environmental exposures). For a given individual, some causes have happened in the past, and are no longer happening, but their damage trail remains. Other causes are ongoing, have caused damage, and continue to cause damage.

Why would anyone expect a human being with such a toxic history to respond to a potential treatment the same way that a laboratory animal raised in a controlled environment would respond to that treatment? Furthermore, why would anyone expect a human being with such a toxic history to respond to a potential treatment the same way that another human being without such a toxic burden would respond to that treatment?

Consider the previous example of Dr. Terri Wahls, an M.D. who was able to reverse her own case of MS [Kostoff, 2012; Kostoff, 2015]. She used two main types of treatments: lifestyle changes (mainly dietary) to reverse the MS and NMES to reverse the damage resulting from MS. **It was only when her diet achieved substantial improvement that the NMES produced positive effects.**

While Dr. Wahls' experience represents one data point only, it is a very powerful data point. Consider its implications. Suppose a clinical trial were conducted to evaluate the potential for NMES to reverse the damage from MS. Suppose further that Dr. Wahls' dietary-dominant contributing

factor to MS and her reaction to NMES were typical of the participants in such a clinical trial. If the participants did not address their diet (with the rigor shown by Dr. Wahls) during the clinical trial, they would not respond positively to the NMES (as was the case for Dr. Wahls initially). **The trial would be interpreted as a failure of NMES**. However, in this hypothetical example, the NMES ineffectiveness is not the reason for the clinical trial's lack of success. ***Failure to remove the cause of the disease and subsequent damage is the problem!*** Failure to remove cause (of the three chronic diseases) as a reason for the very limited success of myriad treatments in the clinical trials of the past three decades cannot be ruled out.

That is why even so-called 'failed' treatments were included in the studies of the three chronic diseases. It cannot be stated conclusively which treatments failed because 1) they were intrinsically ineffective or 2) their beneficial effects were overwhelmed by the strong negative effects of the ongoing causes remaining operable. In fact, it is unknown whether ***comprehensive, timely, and thorough removal of the relevant contributing factors for each of the three diseases by themselves would have obviated the need for many of these treatments***!

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2. LESSONS LEARNED

2A. Methodology

There was no single method that provided the full spectrum of contributing factors or treatments or biomarkers for any of the diseases studied. Each of the methods used added new information. There were four categories of approaches used to identify contributing factors, treatments, and biomarkers, and future studies should select at least one approach from each category for comprehensiveness.

2A1. Visual Inspection

The text mining software [Vantage Point, 2019] used for the studies would import the Medline records retrieved for the study, and would parse the records in myriad ways, including all phrases in the Title and Abstract and the numbers of records in which they appeared. The visual inspection approach consisted of reading the highest frequency Abstract phrases, and assigning them to contributing factor, treatment, biomarker, and other categories of interest. Usually, the highest frequency 30,000 phrases were examined and binned (where appropriate), which meant that the mainline contributing factors, treatments, and biomarkers were identified. Because the Abstract usually contained millions of phrases (all single, double, triple, and quadruple word phrases in the Abstract), that meant the vast majority of contributing factors, treatments, and biomarkers would have to be identified by other means.

2A2. MeSH

One or both of the MeSH Headings or MeSH Qualifiers was used to target records of interest in each of the three chronic disease studies. If the MeSH Headings were used, those that unambiguously reflected contributing factors, treatments, and biomarkers were selected (depending on the desired target), and the records in these unambiguous MeSH Heading categories were retrieved. The records were read, and the desired information extracted. If the MeSH Qualifiers were used to target records of

interest, those that unambiguously reflected contributing factors, treatments, and biomarkers were selected (depending on the desired target), and the records in the MeSH Qualifier category were retrieved. The records were read, and the desired information extracted. Effectively, the MeSH Headings and MeSH Qualifiers served as linking terms to high information records.

2A3. Text

To identify candidate contributing factors, treatments, and biomarkers in the lower frequency portion of the parsed Abstract field, and to fill in the gaps because 1) not all Medline records have been assigned MeSH terms or 2) the assigned MeSH terms are incomplete, a text-based approach was necessary. Linking terms strongly associated with contributing factors, treatments, and biomarkers were generated through visually inspecting many records containing foundational contributing factors, treatments, and biomarkers in the Titles, and identifying those (typically) non-technical terms that appeared frequently with the foundational contributing factors, treatments, and biomarkers. The remainder of the parsed Abstract field was searched with use of these linking terms. The additional candidate contributing factors, treatments, and biomarkers were extracted from the retrieved phrases, and validated as contributing factors, treatments, and biomarkers.

2A4. Dot Product

This is essentially a text-based approach, and involves intersecting two lists of phrases. It was used for identifying contributing factors only. While the visual inspection approach identifies comprehensively the higher-frequency foundational causes, the linking term approach is less efficient. Not all foundational causes are associated with the finite list of linking terms used. Even if a foundational cause is associated (in the same Abstract) with a linking term, the software effectively limits the proximity of the linking term/foundational cause to four words. Some foundational causes can be located much further away from a linking term than four words in an Abstract.

To identify additional foundational causes that may have slipped through the cracks from the visual inspection and linking term approaches, the dot product approach was developed. Over 12,000 potentially toxic substances from myriad other sources (including past foundational causes studies, government-approved lists of toxic substances, MeSH-derived causes, etc) were generated, and intersected with the millions of Abstract phrases in the core chronic disease literature. Those phrases in common between the two lists were then validated as foundational causes. While the dot product approach was developed specifically for identifying causes, a similar approach could be used for identifying treatments, biomarkers, mechanisms, etc. Moreover, given that many authors don't place detailed substances in the Title or Abstract, there could be substantial benefits gained by using full-text rather than Abstracts.

2A5. Specific Methodologies

The detailed approach used to identify contributing factors, treatments, and biomarkers for the: 1) CKD study is shown in Appendix 1; 2) Pervasive Causes of Disease study is shown in Appendix 2; 3) AD study is shown in Appendix 3; 4) PN/PAD study is shown in Appendix 4.

2B. Results

2B1. Contributing Factors to Disease

Many hundreds of foundational contributing factors were identified for each disease examined. Appendix 5 contains an extensive presentation of the contributing factors to AD. It is similar to the structure and quantity of contributing factors to the other chronic diseases. Appendix 6 contains a taxonomy of impacts from AD foundational contributing factors. This structure is similar to the impacts from other chronic disease contributing factors.

2B2. Treatments for Disease

Many hundreds of treatments were identified for each disease examined. Appendix 7 contains a comprehensive list of the treatments for AD, and Appendix 8 contains a table of treatment benefits for AD. These are similar to the quantity of treatments and treatment impacts for the other chronic diseases.

2B3. Biomarkers and Symptoms

Many hundreds of biomarkers, and somewhat less symptoms, were identified for each disease examined. Appendix 9 contains a table of biomarkers for PN/PAD, followed by a table of symptoms for PN/PAD. These are similar to the types and quantity of biomarkers and symptoms for the other chronic diseases examined.

2B4. Patterns in Contributing Factors to Disease

From my perspective, the dominant finding from the three chronic disease studies and the large Pervasive Causes of Disease study was the large number and wide spectrum of contributing factors to each disease. The challenge was to identify any underlying structures in this voluminous data, and ascertain whether any messages could be gleaned that would support development of protocols to prevent and reverse these diseases.

It became clear that a first-order categorization of the contributing factors could be achieved mechanistically. The contributing factors were divided into six categories (with some overlap): Lifestyle; Iatrogenic; Biotoxins; Occupational/Environmental; Psychosocial/Socioeconomic; Genetics. The latter category was not pursued further, since the thrust of the contributing factors was foundational contributing factors (those tangible causes over which we had (in theory) some control). The categories proved useful for presenting results.

The next question was whether there were a few latent categories that would explain the larger structure. It soon became evident that the bulk of contributing factors to disease were 1) the products of modern and semi-modern technology, especially technology that was effectively unregulated, and from 2) the spinoffs of this modern technology (such as sedentary living, staring at computer screens all day, etc). The problem can be stated summarily as follows:

DIRECT TECHNOLOGY

Direct Technology (the degree of direct impact of technology on foundational causes) plays a strong role in Lifestyle, Iatrogenic, and Occupational/ Environmental foundational causes. In addition, through its impact on the immune and other critical systems, modern technology may play a role in whether exposure to bacteria and viruses translates to symptoms and diseases. Modern technology impacts the growing, processing, and preparation of foods, and many of the adverse effects identified in the Pervasive Causes of Disease eBook can be traced back to the use (mis-use) of technology in the food cycle. The Iatrogenic adverse effects of modern technology result mainly from the high-technology-based drugs, surgery, diagnostics, and therapy that characterize much of modern medicine today. The Occupational/Environmental adverse effects result mainly from the employment of modern technology in commerce, the environment, and the workplace.

INADEQUATE REGULATION

Inadequate Regulation is coupled strongly to the introduction of high technology in all aspects of life. Many of the problems with foods derive from relatively unregulated chemicals, materials, and other contaminants entering the food supply during agriculture and animal husbandry. Many of the Occupational/Environmental exposures arise from relatively unregulated harmful substances entering the workplace and the environment. This is especially true in less developed countries, but occurs in more developed countries as well. Many of the Iatrogenic problems could be traced to drugs, diagnostics, therapies, and other procedures entering practice with insufficient front-end long-term testing (especially testing on humans), and inadequate evaluation of side-effects.

Two major aspects of Inadequate Regulation revolve around insufficient safety: inadequate safety data gathering, and inadequate safety testing. Much of the adverse impact data gathering tends to be from passive surveillance systems, where response rates can be an order of magnitude (or more) less than real-world incidence rates. Pre-market testing, in many cases, suffers from inadequate sample sizes, unrepresentative samples, insufficient long-term testing, and insufficient combination testing to identify potential synergistic effects. Insufficient long-term testing on humans is particularly troubling, since many serious diseases such as AD may have decadal latency periods from specific toxic stimuli. Transgenerational effects could not be excluded without appropriate long-term testing.

Additionally, results from animal testing (which could be long-term from the perspective of many short-lived animals used in testing) do not necessarily translate to human outcomes. First, there is a species difference, and impacts on one species do not necessarily carry over to the same types of impacts on another species. Second, laboratory animals are raised in relatively pristine environments, and subjected to a very few toxic substances during studies on disease contributing factors. Conversely, humans experience many of the contributing factors identified in Pervasive Causes of Disease, and the synergy from these combinations would not have been replicated in the laboratory animal testing.

2B5. Setting Priorities for Preventing and Reversing Chronic Diseases

Our most recent chronic disease study was for PN/PAD. Its core literature was not nearly as large as that of the CKD and AD studies, yet substantially more contributing factors, treatments, and biomarkers were found relative to the CKD and AD studies. I attribute that to the experience gained in identifying these quantities from having performed the CKD and AD studies, and to the improvements made in the identification algorithms.

It is clear that future studies of major chronic diseases will generate at least the levels of numbers obtained in the PN/PAD studies (on the order of 1,000 each of contributing factors, treatments, and biomarkers), and perhaps far more if the studies are resourced adequately. Given these voluminous numbers, some type of priority will need to be assigned to 1) contributing factors to eliminate, 2) biomarkers to be used for diagnostics, and 3) treatments to be implemented, 4) in order to make the treatment protocol feasible for clinicians.

2B5a. Contributing Factors Priorities

Contributing factors differ in myriad ways, but two are of interest here: ease of identification, and ease of elimination. Many aspects of diet, recreational substance use, amount of exercise, etc, are examples of contributing factors that are easy to identify. Exposure to environmental and workplace toxic substances require targeted measurements, and are far more difficult to identify. Dietary substances, recreational drugs, etc, are (in theory) easy to eliminate. Toxic exposures not being measured are impossible to eliminate. Other toxic exposures in the residential area and in the workplace that one cannot avoid (because they can't afford to move or change jobs) are difficult to eliminate.

Our three chronic disease studies resulted in development of a five-step protocol. The protocol is shown in summary form for AD in the following table, but applies to any chronic disease:

FIVE-STEP TREATMENT PROTOCOL TO REVERSE AD

Step 1: Obtain a detailed medical and habit/exposure history from the patient.
Step 2: Administer written and clinical performance and behavioral tests to assess the severity of the higher-level symptoms and degradation of executive functions
Step 3: Administer laboratory tests (blood, urine, imaging, etc.)
Step 4: Eliminate ongoing AD contributing factors
Step 5: Implement AD treatments

For chronic disease, one or more abnormalities in different test results will emerge from Steps 1-3. In theory, the contributing factors can be matrixed against biomarkers, symptoms, etc, to ascertain which factors are contributing heavily to the abnormalities. Unfortunately, the results are not that clear-cut. Consider a matrix of contributing factors against biomarkers, specific and general. For general biomarkers, such as inflammation and oxidative stress, there could be hundreds of contributing factors that impact these general biomarkers. For some specific biomarkers, such as excess mercury, the contributing factor linkage is much clearer and easier to eliminate. While there would probably be health benefits if the hundreds of contributing factors to inflammation and oxidative stress were

eliminated, changes on that order of magnitude are probably not realistic. Additionally, if a person has to be instrumented to ascertain whether he/she is being exposed to the unmeasured contributing factors, that would require a long and expensive process in today's environment.

In the AD and PN/PAD studies, an alternative prioritization approach was recommended. The concept is to initiate the contributing factor elimination process by eliminating those factors 1) identified in the study and 2) easiest to eliminate and 3) under one's control (more or less). I called this eliminating the "low-hanging fruit". These contributing factors had been identified in all three chronic disease studies, and in the Pervasive Causes of Disease study. I suspect they will appear in most major chronic disease studies, but that could be easily checked when these studies are completed. The following table contains the latest incarnation of the "low-hanging fruit" contributing factors:

"LOW-HANGING FRUIT" RECOMMENDATIONS

1) curb the dietary excesses, and remove the dietary deficiencies, identified in the contributing factors list, the medical questionnaire, and the lab tests;
2) eliminate food additives to the extent knowable and possible, including those dietary excesses that derive from food additives (excessive fat, sugar, salt);
3) minimize high temperature cooking and the subsequent increases in advanced glycation end products from certain susceptible foods, heterocyclic amines, acrylamide, and polycyclic aromatic hydrocarbons;
4) reverse the sedentary behavior patterns identified;
5) remove the foundational impediments to better sleep;
6) eliminate the use of 'recreational' drugs, including smoking and excessive alcohol;
7) eliminate the use of medicinal drugs shown in the potential contributing factors list, unless these drugs are absolutely necessary;
8) minimize exposures to some hydrocarbons, such as n-hexane, methyl-n-butyl ketone, carbon disulfide, acrylamide, ethylene oxide, trichloroethylene, kerosene, polycyclic aromatic hydrocarbons (including those found in smoke), etc;
9) minimize exposures to some neurotoxic solvents, especially organic solvents;
10) minimize inhalation and ingestion exposures to pesticides, herbicides, insecticides, and fungicides;
11) minimize exposures to heavy metals in food, in water, and in the air;
12) minimize exposure to particulates, especially air pollution;
13) minimize exposures to ionizing radiation and non-ionizing non-visible radiation (such as cell phones, cell towers, WiFi, smart meters, etc.);
14) minimize chronic stress (mental/emotional/psychological);

Even in the "low-hanging fruit" list, the first half are much more straight-forward to identify and eliminate than the second half.

2B5b. Biomarkers Priorities

There is a gross mismatch between the thousand or so biomarkers identified in our latest chronic disease studies (and expected in future chronic disease studies) and the number of biomarkers typically used in clinical practice for testing. The identified biomarkers need to be reduced by almost two orders of magnitude (with today's analytical instrumentation and costs) to be acceptable in clinical

practice. Experience from the AD and PN/PAD studies has shown that the relatively modest numbers of general biomarkers identified could serve as a starting point for the reduction process. In the AD study, the hypotheses selected to start the culling process were, for the most part, congruent with the general biomarkers identified (e.g., inflammation, oxidative stress, apoptosis, neurodegeneration, etc). In the PN/PAD study, the main general biomarkers identified were used to start the culling process.

Once the general biomarkers were selected, they were then matrixed against the specific biomarkers, and about three specific biomarkers were selected to represent each general biomarker. This would result in somewhere between 50 and 100 specific biomarkers to be used in the diagnostics tests. If that proves to be too many for some clinicians, then two specific biomarkers could be selected rather than three to represent each general biomarker, and the numbers would drop by about a third.

2B5c. Treatment Priorities

In the chronic disease studies performed so far, there tended to be relatively few treatments universally used by the mainstream medical community. Realistically, I would expect that trend to continue. However, in all cases I examined, there tended to be significant numbers of papers addressing adverse effects ('side-effects') of each of these treatments. They are not without risk. Additionally, when these types of treatments shown to have some risk when tested in isolation are combined with other similar treatments, enhanced risk could result from synergies or additive effects.

The ~1,000 treatments identified in the latest chronic disease study covered a very wide spectrum, and varied significantly in their levels of risk. There was a core of low-risk treatments that impacted most, if not all, of the general biomarkers selected. Elimination of a contributing factor could be viewed as a low-risk treatment. Substitution of a health-promoting habit for a health-degrading habit could be viewed as a treatment. There are many other types of low-risk treatments possible, and they don't involve drugs, radiation, or surgery. The latter could be utilized if the former prove to be insufficient. Similar to the recommended prioritization of contributing factor selection starting with the "low-hanging fruit", my recommended prioritization of treatments starts with low-risk treatments (identified in the study). The following table presents some of these low-risk treatments:

LOWEST-RISK TREATMENTS

- Exercise (such as aerobic exercise, walking, resistance training, treadmill, calisthenics, stretching, balancing)
- Sleep Improvement (such as quiet environment, minimal light, minimal food before bedtime, maintain regular sleep schedule)
- Stress Reduction (such as tai chi, yoga, massage, aromatherapy, accupuncture, accupressure, sensory stimulation, physiotherapy, massage, reflexology, meditation)
- Diet - Choose foods high in
    - polyphenols (such as cloves, star anise, capers, curry powder, ginger, cinnamon, peppermint, oregano, sage, rosemary, thyme, basil, cocoa, tea, red wine, chokeberries, elderberries, blueberries, plums, cherries, black currants, blackberries, strawberries, raspberries, grapes, flaxseeds, celery seeds, chestnuts, hazelnuts, pecans, almonds, walnuts, olives, artichokes, chicory, red onion, spinach, broccoli, apples, pomegranates, peaches, apricots, olive oil, canola oil), especially flavonoids (such as apples, blueberries, strawberries, red grapes, cabbage, broccoli, onions,

capers, dark chocolate, cocoa, tea, red wine), isoflavones/genistein (such as soybeans, natto, tempeh, tofu, miso), and anthocyanins (such as blackberries, black currants, blueberries, strawberries, cranberries, eggplant, cherries, prunes, raisins, and the darker versions of raspberries, cabbage, plums, radish, grapes, plums, apples, beans, beets, cabbage, onions, pears, wines)

- Unrefined carbohydrates (such as whole grains, legumes, fruits, and uncooked vegetables)
- DHA/omega-3 fatty acid (such as salmon, herring, mackerel, anchovy, sardine, trout, shark, swordfish, mussel, sea bass, pollock, whiting, flounder, sole, lobster, halibut, carp, oyster, crab, mullet, tuna, perch, snapper, shrimp, octopus)
- Vitamin B12/Folate (such as meat [beef liver, lamb, beef], fish [sardines, mackerel, salmon], dairy [feta cheese, cottage cheese], eggs, legumes [chickpeas, fermented soy, pinto beans, lentils], fruit [banana, avocado], vegetables [spinach, parsley, broccoli, beets, turnip, asparagus,])
- Vitamin C (such as fruits [guavas, acerola cherry, kiwifruit, rose hips, strawberries, oranges, papayas, vegetables [bell peppers, broccoli, tomatoes, snow peas, kale])
- Vitamin D (such as fish [sardines, salmon, mackerel, tuna], liver [beef, calf, cod liver oil], dairy [milk, yogurt]; most importantly, sunlight on exposed skin)
- Vitamin E (such as seeds [sunflower seeds, pumpkin seeds], nuts [almonds, hazelnuts, pine nuts], fish [abalone, salmon, trout], fruit [avocado, mango, kiwifruit], vegetables [red peppers, turnip greens, spinach, chard, squash, broccoli])
- lycopene (such as tomatoes, guavas, watermelon, papaya, grapefruit),
- oleic acid (such as nuts [almonds, peanuts, pecans, cashews, pistachios, hazelnuts] seeds [sesame, sunflower], avocados, olives, and vegetable oils [safflower, almond, olive, sesame, sunflower]),
- luteolin (such as dried oregano, celery seed, hot peppers, peppermint, sage, rosemary, juniper berries, thyme, radicchio, chinese celery),
- quercetin (such as capers, lovage leaves, elderberry juice, dock leaves, raddish leaves, arugula, dill weed, coriander, and fennel, cilantro, banana peppers, juniper berries, oregano, onions, carob flour, radicchio, red leaf lettuce, onions, watercress, raw, asparagus, kale, okra, cocoa powder, chia seeds)
- sulforaphane (such as broccoli sprouts, broccoli, cauliflower, kale, brussels sprouts, cabbage, collards, arugula, turnips)
- resveratrol (such as red wine, red grapes, peanut butter, pistachios, cocoa powder, dark chocolate, strawberries, blueberries, bilberries, cranberries)
- epigallocatechin-3-gallate (such as green tea, black tea, carob powder, apples, blackberries).

Caveats on diet:

- Many toxic/harmful substances enter the food supply during all phases of food growth, distribution, and processing. While foods should be selected to maximize the amounts of healing nutrients identified above, care must be taken to minimize the level of toxic additions to the food in parallel.

- Low-temperature cooking should be used to minimize production of AGEs and other harmful products (nitrosamines, polycyclic aromatic hydrocarbons, and acrylamides) during the cooking process.
- Only low-mercury wild-caught fish should be used; these tend to be smaller fish, lower on the food chain.
- Grass-fed animals with no exogenous growth hormones or antibiotics should be used, if possible, since these harmful products could be passed through to the consumer.
- For fruits and vegetables normally eaten with skin, those that have not been sprayed with harmful pesticides and other toxic chemicals should be used.
- Heavy metals are a contributing factor for many diseases, especially neurodegenerative diseases. One source of heavy metal bioaccumulation in the body is through the food supply. Heavy metals can occur naturally in the soil in which food is grown, they can concentrate abnormally in soils from nearby industrial pollution or from precipitation of air pollution, they can preferentially absorb in different types of food, and, depending on the type of food, can be absorbed from the food processing and manufacturing process. Any of the above foods selected for chronic disease prevention or treatment/reversal purposes should have heavy metal concentrations as low as possible.

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2C. Mandates

I'm treating this section separate from the results, even though it flows from the results. The central thesis of our treatment protocol for chronic diseases is that contributing factor elimination is a prime requirement for the possibility of preventing and reversing chronic disease. However, the inverse is also true. Contributing factor enhancement is a prime requirement for developing and exacerbating chronic disease.

Unfortunately, there are myriad ways in which contributing factors to disease are imposed on the population by government mandates, loose regulations, and other means. Effectively, government is promoting and, in some sense, mandating the expansion of chronic disease among its population.

Consider the example of non-ionizing radiation technology. This technology has become ubiquitous in modern life (cell phones, WiFi, smart meters, etc.). Research has shown that non-ionizing radiation in the cell phone radiofrequency part of the spectrum contributes to oxidative stress and inflammation of the brain [Kostoff and Lau, 2017; Chauhan, Verma, Sisodia et al, 2017; Kesari, Siddiqui, Meena, 2013], among many other adverse effects. As our chronic disease study results show, oxidative stress and inflammation are key chronic disease characteristics. Chronic exposure to non-ionizing radiation would be a factor contributing to increase the incidence of those many chronic diseases in which these two characteristics are important.

Non-ionizing radiation technology requires an infrastructure. For cell phones, the major infrastructure is cell towers. The Telecommunications Act of 1996 effectively mandates the construction of cell towers with no opposition allowed based on environmental considerations. For example, the

Telecommunications Act of 1996, in Section 704, contains the statement “No State or local government or instrumentality thereof may regulate the placement, construction, and modification of personal wireless service facilities on the basis of the environmental effects of radio frequency emissions to the extent that such facilities comply with the Commission's regulations concerning such emissions” [Telecommunications Act, 1996].

The Spectrum Act of 2012 “facilitates the telecommunications industry’s rapid deployment of wireless infrastructure by requiring local governments to approve any application by a carrier that asks to modify and existing cellular communication structure that does not “substantially change” the existing facility. Section 6409 states cities ““may not deny, and shall approve any eligible facilities request for a modification of an existing wireless tower or base station that does not substantially change the physical dimensions of such tower or base station.” (47 U.S.C. § 1455(a)(1).) Section 6409 defines “eligible facilities request” as “any request for modification of an existing wireless tower or base station that involves –

(a) collocation of new transmission equipment;

(b) removal of transmission equipment; or

(c) replacement of transmission equipment [Spectrum, 2012].”

Thus, “The U.S. Telecommunications Act of 1996 and the Spectrum Act of 2012 limit local government’s ability to place infrastructure for cellular communications and simultaneously facilitates industry deployment [Spectrum, 2012].” For all practical purposes, this means that citizens opposed to cell tower construction cannot use adverse health effects in their arguments.

As of this writing, the FCC is attempting to implement similar effective mandates for the next generation of mobile wireless technology, known as 5G. A million or more 'short' cell towers (in the USA alone) would be required for 5G implementation, since the propagation of radiation energy at the high frequencies characteristic of 5G is poor, and the distance between 'short' cell towers is relatively small by necessity.

This means that populated areas will be blanketed (around the clock) with 3GHz-30GHz (or higher) radiofrequency radiation. This is a range of the frequency spectrum essentially untested for adverse health effects, especially over the long-term in humans, and especially in combination with other toxic stimuli [Kostoff and Lau, 2017]. It is no different in principle from a contractor proposing to spray the populated areas of the USA with Agent Orange around the clock, and the relevant government regulatory agency stating that no opposition to the spraying is allowed based on health considerations.

Thus, we have a dichotomy in the relevant USA Federal policy. On the one hand, the Federal government is investing heavily in biomedical research to treat and reverse many chronic diseases. On the other hand, the Federal government is allowing essentially unrestricted and inadequately regulated expansion of technologies that are important contributing factors to these chronic diseases. Metaphorically, the Federal government is *drilling holes in the floor of the boat at the same time they are pumping water out of the boat*! These policies are diametrically opposed, and will limit the effectiveness of any chronic disease treatment protocol, no matter how strictly followed.

Effectively, the Federal government is promoting/mandating non-ionizing radiation exposure on its citizens, and our chronic disease studies have shown that non-ionizing radiation is a contributing factor to myriad diseases. For all practical purposes, ***the USA Federal government is promoting/mandating an increase in rates of these chronic diseases***, with the potential of this increase being very large.

Another example. I did a study in 2018 examining OSHA's Permissible Exposure Limits (PELs) [Kostoff, 2018]. They are the workplace limits legally enforceable by the Federal government. For the chemicals I selected, I found that the PELs were one to four orders of magnitude higher than those exposures shown in the biomedical literature to cause health damage. For all practical purposes, this functions as a mandate. The government is effectively sanctioning excess exposures that have been shown to cause harm.

The non-ionizing radiation, workplace chemicals, and many other examples where the enforceable exposure limits are orders of magnitude beyond those shown to cause damage are extremely difficult to avoid. For most of these toxic stimuli that have enforceable exposure limits, the public will have no idea whether they are being exposed or not, and what levels of exposure they are experiencing. Thus, a fraction (perhaps substantial) of the contributing factors identified for major chronic diseases cannot be eliminated, for all practical purposes, in today's world. While we now have the knowledge and capability to prevent and reverse many of these chronic diseases with information available today, we are blocked from doing so by a government that is actively promoting those factors that contribute to the development and exacerbation of chronic diseases.

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APPENDICES

APPENDIX 1 – CKD CONTRIBUTING FACTOR AND TREATMENT IDENTIFICATION METHODOLOGY

This appendix is divided into four sections. The first section (1A) describes the query used to retrieve the total CKD core literature. The second section (1B) describes the queries used to retrieve the ***foundational*** causes from the CKD core literature and non-CKD core literature. The third section (1C) describes the queries used to retrieve the treatments from the CKD core literature and non-CKD core literature. The fourth section (1D) describes the queries used to retrieve the symptoms from the CKD core literature.

1A. Overall CKD Core Literature Retrieval Query

The CKD core literature was generated using an iterative process. The term "chronic kidney disease" was inserted into the Topic field in the Thomson version of Medline, and the MeSH terms of the retrieved records were examined for relevancy to the theme of the present study. The most relevant MeSH terms (e.g., Kidney Failure, Chronic; Renal Insufficiency, Chronic; etc) were added to the initial query, and the process repeated. Many retrieved records focused on treatments for the final stages of CKD (dialysis, transplantation, etc), were not matched to the goals of this study (which were essentially to avoid reaching these final stages), and negation terms were added to the query to exclude these dialysis and transplantation records. The final query used to retrieve the CKD core literature was:

"chronic kidney disease" - Text fields

OR

("kidney failure, chronic" OR "renal insufficiency, chronic" OR "Diabetic Nephropathies" OR Nephrosclerosis OR Nephrosis OR Nephritis OR "Nephritis, Interstitial") - MeSH Heading Field

NOT (Renal Dialysis OR Kidney Transplantation OR Peritoneal Dialysis OR Peritoneal Dialysis, Continuous Ambulatory OR Nephrectomy OR Transplantation, Homologous OR Graft Rejection OR Graft Survival OR Dialysis Solutions OR Dialysis OR Hemodialysis, Home OR Hemodialysis Solutions OR Hemodialysis Units, Hospital OR Microdialysis OR Transplantation, Autologous OR Transplantation Immunology OR Transplantation Conditioning OR Transplantation, Heterologous OR Delayed Graft Function OR Kidney Neoplasms OR Renal Replacement Therapy OR Pancreas Transplant OR Neoplasms) - MeSH Heading Field

Time: 1993-2012

1B. CKD Causes Query

At the study's initiation, it was unclear whether more than a CKD core literature analysis would be pursued. The approach used to define causes, treatments, and symptoms from the retrieved CKD core literature consisted of the labor-intensive visual inspection and analysis of MeSH terms and text phrases. When the decision was made to search for cause and treatment *discovery* beyond the CKD core literature, then queries were developed for causes and treatments (and, to a lesser extent, symptoms only in the CKD core literature). These queries were initially applied to the core CKD literature to identify any causes, treatments, and symptoms overlooked by the manually-intensive approach, and the causes and treatments queries were then applied to the non-CKD literature to search for potential discovery. ***The development of these queries, especially the comprehensive foundational 'causes' identification queries, constitutes the main information technology advance of this study.***

1B1. Non-query approaches to CKD core literature causes

The first step in identifying foundational causes from the CKD core literature was a manually intensive approach. The higher frequency MeSH terms associated with the CKD core literature records were examined, and those that appeared to relate to foundational causes were evaluated for relevance. Nominally, ten records that contained each candidate causes MeSH term were examined, and if relevance was about 70% or beyond, the MeSH term was selected. In borderline cases, more MeSH terms were sampled until definitive conclusions could be drawn. Relevant does not mean unanimity or consensus was achieved for either causes or treatments. For causes especially, non-agreement with the majority could have been attributable to poor research, research with a pre-determined agenda (e.g., [14]), or selection of a 'window' in parameter space different from where the cause was operable. But, if cause was found operable in a few of the sampled papers for a given MeSH term, the term was deemed sufficiently important to select.

These higher frequency MeSH terms were then matrixed with all MeSH terms in the retrieval, lower frequency MeSH term candidates were identified through strong co-occurrence, and subsequently validated. Then, a separate database was generated consisting of all the records that included these high and low frequency selected MeSH terms. In this new database, the higher frequency Abstract phrases were examined, and those that appeared to relate to causes were evaluated for relevance. A similar procedure to that used for causes MeSH term selection was followed. The higher frequency Abstract phrases, and some generic Abstract phrases related to causes (e.g., expos*, induc*, etc), were matrixed with all Abstract phrases to identify lower frequency phrase candidates through strong co-occurrence.

Eventually, all the MeSH terms were read and examined, and a few low frequency terms that were missed with the co-occurrence procedure were added to the list. The same was not possible with the Abstract phrases. While there was a total of about 10,000 MeSH terms (readable, although visually intensive), there were millions of Abstract phrases. When the 'causes' queries were developed for the non-CKD literature, they were initially applied to the CKD core literature, and further causes were identified that had been missed with the MeSH and Abstract phrase procedures. Because of the proximity nature of the 'causes' queries, and the inability of Pubmed to accept proximity queries, these queries were applied to Thomson Medline to identify the additional causes.

As stated in the Introduction, only ***foundational causes*** were evaluated in this study. There were five main types of foundational causes: genetics, iatrogenic, biotoxic, environmental exposure, and lifestyle. Since the purpose of this study is to identify specific causes to eliminate and treatments to pursue to prevent/halt/reverse CKD, and since relatively little can be done at this time to alter the genetics foundational causes, the genetics causes were not included in the final queries.

1B2. Initial CKD core literature causes query

Query=#1 AND (#2 OR #3)

(terms defined below)

After the CKD core literature causes MeSH terms and phrases had been identified through the manual processes, an initial causes query, applicable only to the CKD core literature, was developed. It had two purposes: identify causes overlooked by the manual procedures, and serve as a precursor to a more complex query applicable to all literatures, CKD and non-CKD alike.

The overall query structure was of the generic form [Cause][Produces][Symptom]. Two of the three would be specified in the query, directly or implicitly, and the retrieval would provide the third. Examples from causes query:

a. Cause near Produces: steroid-induc* or diet-induc* OR antibiotic near/1 cause*. These are generic or specific members of classes of potential causes in proximity to Produces-type terms. The classes tend to be drugs, diets, etc. The Produces-type terms are necessary since drugs, diets, etc can be either beneficial or harmful, depending on circumstances.

b. Produces near Symptom: cause* near/5 "renal damage" NOT "renal damage cause*"

c. Cause near Symptom: *Bacterium or pentachloro* in title, with either Symptom in title or in MeSH. If we go to Abstracts, we need stronger proximity condition; e.g., *Bacterium near/5 Symptom. Unlike case 1, in this case the causes are specific members of classes of potential causes that usually don't have beneficial effects, and therefore don't require proximity to causes-like terms; the causative nature is implied by the substance.

Note on the above. We have used [cause-produce-symptom] as the model, but a somewhat broader form could be: [cause-produce-adverse effects], of which Symptom is one way of describing an adverse effect. Thus, 'toxic*' or 'adverse effect*', or 'harm*' in the title by itself, along with the Symptom in the title or MeSH tends to be accompanied by the cause and the effect it has.

Additionally, many research articles addressing causes (and treatments) use the language [cause/treatment-activates/inhibits/blocks-signaling pathway(s)] (e.g., "Houttuynia cordata Thunb inhibits the production of pro-inflammatory cytokines through inhibition of the NFkappaB signaling pathway in HMC-1 human mast cells."; "Vitexin protects against cardiac hypertrophy via inhibiting calcineurin and CaMKII signaling pathways"; "MicroRNA-222 promotes tumorigenesis via targeting DKK2 and activating the Wnt/beta-catenin signaling pathway"). The signaling pathways were not used as part of the queries in this study, but a future more comprehensive and well-resourced study could include the signaling pathways in the queries; their incorporation would be straight-forward. Many research papers, especially at the more fundamental biological level, may not mention diseases or symptoms, but

are written in the language of effects on signaling pathways, and these papers could be accessed by the appropriately-written queries.

The query below has three main components: #1 is the overall CKD retrieval, #2 is the MeSH component and #3 is the text (phrases) component. Components #2 and #3 are intersected with component #1. While #2 and #3 contain genetics retrieval terms, these parts of the retrieval were not used for the analysis. The causes identified from the prior manual procedures were used as negation terms in the query, to minimize extraneous retrieval.

1. OVERALL CKD CORE LITERATURE RETRIEVAL

("kidney failure, chronic" OR "renal insufficiency, chronic" OR "Diabetic Nephropathies" OR Nephrosclerosis OR Nephrosis OR Nephritis OR "Nephritis, Interstitial") - MeSH Heading Field in Thomson Reuters

OR "chronic kidney disease" - Topic Field

NOT

(Renal Dialysis OR Kidney Transplantation OR Peritoneal Dialysis OR Peritoneal Dialysis, Continuous Ambulatory OR Nephrectomy OR Transplantation, Homologous OR Graft Rejection OR Graft Survival OR Dialysis Solutions OR Dialysis OR Hemodialysis, Home OR Hemodialysis Solutions OR Hemodialysis Units, Hospital OR Microdialysis OR Transplantation, Autologous OR Transplantation Immunology OR Transplantation Conditioning OR Transplantation, Heterologous OR Delayed Graft Function OR Kidney Neoplasms OR Renal Replacement Therapy OR Pancreas Transplant OR Neoplasms) - MeSH Heading Field

AND

2. MESH COMPONENT

("/chemically induced" OR /toxicity OR /poisoning OR /congenital OR "kidney failure, chronic/genetics" OR "renal insufficiency, chronic/genetics") - MeSH Heading field

OR

("Genetic Predisposition to Disease" OR "Smoking" OR "Polymorphism, Single Nucleotide" OR "Gene Frequency" OR "Alleles" OR "Aluminum" OR "Diphosphonates" OR "Gadolinium DTPA" OR "Sodium, Dietary" OR "Heterozygote" OR "Genetic Linkage" OR "Disease Susceptibility" OR "Haplotypes" OR "Sodium Chloride, Dietary" OR "Collagen Type IV" OR "Mutation, Missense" OR "Familial Mediterranean Fever" OR "Environmental Exposure" OR "Food Habits" OR "Aristolochic Acids" OR "Alcohol Drinking" OR "Substance-Related Disorders" OR "Lead" OR "Linkage Disequilibrium" OR "Amino Acid Substitution" OR "Occupational Exposure" OR "Infant, Low Birth Weight")

OR

("Occupational Diseases" OR "Cadmium" OR "Alcoholism" OR "Birth Weight" OR "Dehydration" OR "Fruit" OR "Lead Poisoning" OR "Carcinogens" OR "Genetic Association Studies" OR "Prenatal Exposure Delayed Effects" OR "Environmental Pollutants" OR "Nicotine" OR "Environmental Monitoring" OR

"Solvents" OR "Phenacetin" OR "Cocaine" OR "Silicon Dioxide" OR "Arsenic" OR "Metals, Heavy" OR "Hydrocarbons" OR "Mycotoxins" OR "Pesticides" OR "Cadmium Poisoning" OR "Silicosis" OR "Amphetamines" OR "Hallucinogens" OR "Inhalation Exposure" OR "Insecticides" OR "Organic Chemicals" OR "Aflatoxins" OR "Arsenic Poisoning" OR "Phenylenediamines") - MeSH Heading no Explode field

2. TEXT COMPONENT

(gene OR genes OR genetic* OR Polymorphism* near/5 "Single Nucleotide*" OR Allele* OR Heterozygote* OR "Collagen Type IV" OR Mutation* OR "Linkage Disequilibrium" OR "Amino Acid" near/5 Substitut* OR congenital OR Low* near/5 "Birth Weight*" OR familial OR hereditary OR heritable) OR (nephrotoxi* OR poison*) OR ((toxi* near/25 (drug* OR aluminum OR expos* OR "contrast agent*" OR nephropathy OR cisplatin OR antibiotic* OR anesthetic* OR occupation*)) NOT (uremic* OR uraemic))

OR

("renal injury" OR "renal damage" OR "renal failure" OR "renal insufficiency" OR "renal disease" OR "kidney injury" OR "kidney damage" OR "kidney failure" OR "kidney disease" OR nephropath*) near/75 (expos* near/15 (contrast OR nephropath* OR occupation* OR nephrogen* OR drug* OR aluminum OR environment* OR intoxication OR gadodiamide OR gadolinium OR cadmium OR solvent* OR herb* OR hydrocarbon* OR industr* OR silicosis OR tenofovir OR silica OR antiretroviral* OR statin* OR (angiotensin near/3 (inhibitor* OR blocker*)) OR cadmium OR fluoride* OR "heavy metal*" OR chloroform OR copper OR chromium OR mercury OR prenatal OR inhal* OR chemical*))

OR

(analges* OR acetaminophen OR nsaid* near/50 (necrosis OR nephritis OR nephropath*) OR Phenacetin* OR Diphosphonate* OR adenine OR adriamycin OR doxorubicin OR "contrast agent*" OR "contrast medium" OR "Aristolochic Acid*" OR arsenic OR "Lead exposure" OR "blood lead" OR "lead burden" OR "environmental lead" OR Occupation* near/50 (silica OR solvent* OR hydrocarbon* OR fiberglass OR herbalist* OR "heavy metal*" OR poison*) OR Dehydrat* OR "star Fruit" OR Environment* near/50 Pollut* OR Solvent* OR Hydrocarbon* OR "Ethylene glycol")

OR

(lithium near/5 (nephrogen* OR intoxicat* OR induc* OR nephropath*) OR puromycin OR rapamycin OR acyclovir OR Pesticide* OR Insecticide* OR Chemical* near/5 induc* OR Aflatoxin* OR Phenylenediamine* OR Smok* OR high-Sodium OR high-salt or "sodium intake" OR "dietary sodium" OR "dietary salt" OR "dietary phosphorous" OR "protein intake" OR "dietary acid*" OR Cocaine OR heroin OR Amphetamine* OR Hallucinogen* OR Alcoholi* OR Nicotine OR Alcohol near/5 (consumption OR abuse* OR intake OR Drink* OR expos*) OR Substance near/5 abuse* OR "advanced glycation") - Topic

1B3. Final CKD core literature causes query

The following is the final all-literature causes query applied specifically to the CKD core literature. The overall retrieval term was treated differently, to be consistent with the overall CKD retrieval term defined for the study.

Query=#1 AND (#2 OR #3 OR #4), where these numbers are defined below.

Element #1 is the retrieval for overall CKD, and was defined in the previous section.

The three query components that follow (all of which are intersected with Element #1) are designed to extract/filter only those records that identify foundational causes from the retrieval generated by Element #1. The design of these query components was based on the assumption that foundational causes will have the following form: [Cause][Produces][Symptom]. Various combinations of Cause/Produces/Symptom may be used (e.g., Cause near Symptom, Produces near Symptom, Cause near Produces, etc), and all will provide complementary retrievals, with some degree of overlap.

Element #2 can be interpreted as having two text (phrases) components: a specific high-Precision component and a generic high Recall component. The two components complement each other. The specific component consists of names of drugs, chemicals, viruses, bacteria, etc. The specific drug and chemical terms used for the query were selected from lists of highly toxic drugs and chemicals. Numerous experiments showed that when these types of terms appeared in the title, they were usually there as causes. The addition of many more such terms is possible, subject only to query length limitations. Most of these terms could be viewed as being in the 'environmental exposures' category. This is an example of the Causes near Symptom combination mentioned above. There were also some moderately generic terms like steroid-induc* or diet-induc*, which were examples of the Causes near Produces combination mentioned above.

The generic component consists of proximity condition terms like cause* near/5 "renal damage", accompanied by negation terms of the form NOT "renal damage cause*". Thus, this component retrieves unrestricted causes of renal damage, and the negation terms eliminate those cases where 'renal damage' is the cause. Initially, only phrases like "cause renal damage" were used, but the flexibility allowed by the proximity condition combined with the negation terms expanded the retrieval Recall substantially, with only a modest drop-off in Precision. The causes identified here are examples of the Produces near Symptom combination mentioned above.

Element #2 could have ranged from title to full text, but stricter proximity conditions would have had to be employed beyond title to insure high Precision. In its present form, Element #2 was applied to title phrases only, but in a 'production run', could easily be expanded to other text fields using more stringent proximity conditions.

Element #3 consisted of MeSH Qualifiers focused on causes. If high Recall were desired, other Qualifiers, such as Adverse Effects or Pathogenicity, could be used, albeit with possibly reduced Precision. Combinations of Qualifiers were not examined extensively, although in a 'production run', combinations would undoubtedly provide additional Recall with reasonable Precision. Qualifiers like Etiology might be more effective in combination.

Element #4 consisted of relatively generic causes MeSH terms. They tended to be examples of Causes near Symptoms combinations described above. Initially, much broader and higher level MeSH terms were used for this component, in the MeSH Heading Explode Medline mode. The retrieval would 'time out' when these broader terms were used. The final list of MeSH terms shown in query Element #4 was a sub-set of the MeSH terms that had been generated by visual inspection of all the MeSH phrases in the

core CKD retrieval, augmented by a few related MeSH terms from the Medline taxonomy tree. Since these MeSH terms were obtained initially from the MeSH Headings in their No Explode configuration, it was decided to access this field only. Restricting these terms to the MeSH Heading No Explode field eliminated the 'time out' problem, and provided the highest Precision/relevance, albeit at the expense of Recall.

In a 'production run', if higher Recall is desired, and sufficient computer power is available along with an in-house version of Medline, the higher level MeSH terms could be employed along with the Explode option.

In summary, many query options are available, depending on the objectives of the study, the degree of Precision/Recall desired, and the resources available for data retrieval and analysis. We have described only a few above; other experiments were performed using intersections of Elements #2, #3, and #4, as well as with the higher level MeSH terms. These combinations again yield high Precision at the expense of Recall. Finally, the causes identified from the manual procedures initially, and the additional causes identified with the initial CKD core literature causes query, were used as negation terms to minimize extraneous retrieval for the final CKD core literature causes query.

Query Elements

1. **TITLE PLUS MESH**

("kidney failure, chronic" OR "renal insufficiency, chronic" OR "Diabetic Nephropathies" OR Nephrosclerosis OR Nephrosis OR Nephritis OR "Nephritis, Interstitial") - MeSH Heading Field in Thomson Reuters

OR "chronic kidney disease" - Topic Field

NOT

(Renal Dialysis OR Kidney Transplantation OR Peritoneal Dialysis OR Peritoneal Dialysis, Continuous Ambulatory OR Nephrectomy OR Transplantation, Homologous OR Graft Rejection OR Graft Survival OR Dialysis Solutions OR Dialysis OR Hemodialysis, Home OR Hemodialysis Solutions OR Hemodialysis Units, Hospital OR Microdialysis OR Transplantation, Autologous OR Transplantation Immunology OR Transplantation Conditioning OR Transplantation, Heterologous OR Delayed Graft Function OR Kidney Neoplasms OR Renal Replacement Therapy OR Pancreas Transplant OR Neoplasms) - MeSH Heading Field

AND

2. **TITLE PHRASES**

((Amiodarone OR Antipsychotic* OR "anti-infective*" OR antiadrenergic OR antiandrogen* OR antianginal OR antiarrhythmic OR antiasthmatic OR antibiotic* OR antineoplastic* OR antiemetic* OR anticholinergic* OR antispasmodic* OR anticoagulant* OR anticonvulsant* OR antidepressant* OR antidiarrheal* OR antiemetic OR antivertigo OR antifungal* OR antigonadotropic OR antigout OR antihistamine* OR antimalarial OR antimetabolite* OR antimigraine OR antiparkinson OR antiplatelet OR antipseudomonal OR antipsoriatic* OR antirheumatic* OR antiseptic OR germicide* OR antitoxin*

OR antivenin* OR antituberculosis OR antitussive* OR antiviral OR Azole* OR Barbiturate* OR Bleomycin OR "Calcium Channel Blocker" OR Chloramphenicol OR Chlorpromazine OR Digitalis OR Haloperidol OR Halothane OR Ketoconazole OR Metronidazole OR Niacin OR Nitroglycerin OR Primaquine OR Sulfonamide* OR Tamoxifen OR Thioridazine OR Tricyclics OR "Valproic Acid") near/1 (caus* OR induc*)) OR ("*toxic" OR "*toxici*" OR "toxicologic*" OR "toxica*" OR "poison*" OR contamina* OR "adverse* effect*" OR "side effect*" OR "deleterious effect*" OR "negative effect*" OR "detrimental effect*" OR diet* near/1 effect* OR "ecotoxologic* effect*" OR particulate* near/1 effect* OR "adverse reaction*" OR "adverse food" OR "adverse drug" OR "adverse health" OR "expos*" OR "additives" OR "chemicals" OR "abuse*" OR "harm" OR "harms" OR "harmful" OR "aggravate*" OR "occupation*" OR "intoxicat*" OR pollut* OR "*virus*" OR antibiotic* OR environmental OR drug*-induc* OR chemotherapy-induc* OR treat*-induc* OR stress-induc* OR chemical*-induc* OR cytokine*-induc* OR exercise-induc* OR surg*-induc* OR diet*-induc* OR radiation-induc* OR steroid-induc* OR mechanically-induc* OR "damage-induc*" OR "damage-caus*" OR drug*-caus* OR chemotherapy-caus* OR treat*-caus* OR stress-caus* OR chemical*-caus* OR cytokine*-caus* OR exercise-caus* OR surg*-caus* OR diet*-caus* OR radiation-caus* OR steroid-caus* OR mechanically-caus* OR *OBACTER OR Chlamydia OR Chlamydophila OR Clostridium OR *Bacterium OR *Chia OR *Ococcus OR Haemophilus OR Mycoplasma OR Neisseria OR *Omonas OR Rickettsia OR Rochalimaea OR marcescens OR Treponema OR Vibrio OR Yersinia OR *benzene OR trichloro* OR hexachloro* OR dichloro* OR tetrachloro* OR parachloro* OR dinitro* OR pentachloro* OR polychlor* OR *phthalate OR *ethane OR *toluene OR *nitrophenol* OR perfluor* OR polyfluor* OR polybrom* OR hexabrom* OR decabrom* OR tetrabrom* OR waterborne OR "water-borne" OR dietborne OR "sediment-associated" OR "particle-associated" OR "traffic-related" OR "work-related") OR ((caus* near/5 ("renal injury" OR "renal damage" OR "renal failure" OR "renal insufficiency" OR "renal disease" OR "kidney injury" OR "kidney damage" OR "kidney failure" OR "kidney disease" OR nephropath*) OR induc* near/5 ("renal injury" OR "renal damage" OR "renal failure" OR "renal insufficiency" OR "renal disease" OR "kidney injury" OR "kidney damage" OR "kidney failure" OR "kidney disease" OR nephropath*) OR produc* near/5 ("renal injury" OR "renal damage" OR "renal failure" OR "renal insufficiency" OR "renal disease" OR "kidney injury" OR "kidney damage" OR "kidney failure" OR "kidney disease" OR nephropath*)) NOT ("renal injury caus*" OR "renal damage caus*" OR "renal failure caus*" OR "renal insufficiency caus*" OR "renal disease caus*" OR "kidney injury caus*" OR "kidney damage caus*" OR "kidney failure caus*" OR "kidney disease caus*" OR "nephropath* cause*" OR "caused by renal injury" OR "caused by renal damage" OR "caused by renal failure" OR "caused by renal insufficiency" OR "caused by renal disease" OR "caused by kidney injury" OR "caused by kidney damage" OR "caused by kidney failure" OR "caused by kidney disease" OR "caused by nephropath*" OR "renal injury induc*" OR "renal damage induc*" OR "renal failure induc*" OR "renal insufficiency induc*" OR "renal disease induc*" OR "kidney injury induc*" OR "kidney damage induc*" OR "kidney failure induc*" OR "kidney disease induc*" OR "nephropath* induc*" OR "induced by renal injury" OR "induced by renal damage" OR "induced by renal failure" OR "induced by renal insufficiency" OR "induced by renal disease" OR "induced by kidney injury" OR "induced by kidney damage" OR "induced by kidney failure" OR "induced by kidney disease" OR "induced by nephropath*" OR "renal injury produc*" OR "renal damage produc*" OR "renal failure produc*" OR "renal insufficiency produc*" OR "renal disease produc*" OR "kidney injury produc*" OR "kidney damage produc*" OR "kidney failure produc*" OR "kidney disease produc*" OR "nephropath* produc*"))

3. MESH QUALIFIERS - MESH HEADING

(/"chemically induced" OR /toxicity OR /poisoning)

OR

4. MESH GENERIC TERMS - MESH HEADING NO EXPLODE

Abnormalities, Drug-Induced OR Air Pollutants, Occupational OR Anti-Allergic Agents/adverse effects OR Anti-Asthmatic Agents/adverse effects OR Antibiotics, Antitubercular/adverse effects OR Anticonvulsants/adverse effects OR Antidepressive Agents/adverse effects OR Anti-Infective Agents/adverse effects OR Anti-Infective Agents, Urinary/adverse effects OR Antimanic Agents/adverse effects OR Antineoplastic Agents/adverse effects OR Antipsychotic Agents/adverse effects OR Antipyretics/adverse effects OR Antirheumatic Agents/adverse effects OR Antithyroid Agents/adverse effects OR Antitubercular Agents/adverse effects OR Anti-Ulcer Agents/toxicity OR Anti-Allergic Agents/toxicity OR Anti-Asthmatic Agents/toxicity OR Antibiotics, Antitubercular/toxicity OR Anticonvulsants/toxicity OR Antidepressive Agents/toxicity OR Anti-Infective Agents/toxicity OR Anti-Infective Agents, Urinary/toxicity OR Antimanic Agents/toxicity OR Antineoplastic Agents/toxicity OR Antipsychotic Agents/toxicity OR Antipyretics/toxicity OR Antirheumatic Agents/toxicity OR Antithyroid Agents/toxicity OR Antitubercular Agents/toxicity OR Anti-Ulcer Agents/toxicity OR Congenital Abnormalities OR Congenital Disorders of Glycosylation OR Dermatitis, Occupational OR Drug Eruptions OR Drug Hypersensitivity OR Drug Toxicity OR Environmental Exposure OR Environmental Illness OR Environmental Monitoring OR Environmental Pollutants OR Fast Foods OR Food Additives OR Food Contamination OR Food Habits OR Food Preservatives OR Fossil Fuels OR Glycosylation End Products, Advanced OR Hallucinogens OR Hazardous Substances OR Herbicides OR Household Products OR Hydrocarbons OR Hydrocarbons, Alicyclic OR Hydrocarbons, Aromatic OR Hydrocarbons, Chlorinated OR Hydrocarbons, Fluorinated OR Hydrocarbons, Halogenated OR Iatrogenic Disease OR Inhalation Exposure OR Insecticides OR Leisure Activities OR Marine Toxins OR Maternal Exposure OR Mutagens OR Mycotoxins OR Neurotoxins OR Nonprescription Drugs OR Occupational Diseases OR Occupational Exposure OR Occupations OR Organic Chemicals OR Paternal Exposure OR Pesticides OR Plant Poisoning OR Plants, Toxic OR Poisoning OR Poisons OR Prenatal Exposure Delayed Effects OR Soil Pollutants OR Solvents OR Substance-Related Disorders OR Sweetening Agents OR Vehicle Emissions OR Water Pollutants, Chemical OR Welding

1B4. Non-CKD Core Literature Causes

The causes from the non-CKD literature were generated with use of the final causes query alone. The final query variant used was a tradeoff between Precision, Recall, and sufficient streamlining not to 'time-out' the Web interface with Thomson Medline. Specifically, more comprehensive queries that employed large numbers of Exploded MeSH terms (all MeSH sub-categories are examined when Exploded MeSH terms are used) would 'time out' the retrieval, and could not be used. To reduce the volume of retrieval, both the records from the CKD core retrieval and the causes phrases identified in the CKD core literature causes analysis were subtracted from the retrieval.

The final non-CKD core literature causes query is similar to the final CKD core literature causes query, with the exception that more negation terms are used in the non-CKD case, and a few extra generic terms were added at the end of Element #2. The highlighted terms in 1A (below) are the additional core CKD causes identified in the process of validating discovery. The query is as follows (hypertension used for illustrative purposes):

Query=(#1 NOT (#1a OR #1b OR #1c)) AND (#2 OR #3 OR #4)

1. **TITLE PLUS MESH**

(hypertension)

NOT

1a. TITLE PHRASES

("1-methyl-4-phenylpyridinium ion" OR "2,4,6-trinitrobenzene sulfonic acid" OR "3,4-dideoxyglucosone-3-ene" OR "4-HNE" OR "5-fluorouracil" OR "7-Ketocholesterol" OR "9-hydroxy-2-methylellipticinium" OR "12-O-tetradecanoylphorbol-13-acetate" OR "ablation-induc*" OR "acarbose" OR "ACE inhibitor*" OR "Acetaldehyde" OR "acetaminophen" OR "acetazolamide" OR "acetylcholinesterase-inhibiting pesticide*" OR "acetylsalicylic acid" OR "acidogenic diet*" OR "acrolein" OR "activity restriction" OR "acyclovir" OR "adalimumab" OR "adefovir" OR "adenine" OR "Adenovirus*" OR "adriamycin" OR "adr-induc*" OR "advanced glycation end product*" OR "advanced glycation end product*-oral" OR "Advanced glycosylation end product*" OR "aflatoxin*" OR "Aipysurus laevis venom" OR "air pollutants" OR "alclofenac" OR "alcohol abuse*" OR "alcohol consum*" OR "alcohol intake" OR "alcoholic*" OR "alcohol-induc*" OR "alcoholism" OR "aldrin" OR "alfacidol" OR "aliskiren" OR "allopurinol" OR "alloxan" OR "all-trans-retinoic acid" OR "alpha3-IV collagen" OR "alpha3(IV)-NC1-induced" OR "alpha-mercaptopropionylglycine" OR "aluminium" OR "aluminum" OR "Amanita phalloides" OR "amikacin" OR "aminoglycoside " OR "amiodarone" OR "Amitriptyline" OR "amlodipine" OR "ammonium perchlorate" OR "Amoxicillin" OR "amphetamine*" OR "amphotericin b" OR "Ampicillin" OR "ampiroxicam" OR "anabolic steroid*" OR "ANCA" OR "ang ii-induc*" OR "angiotensin ii-induc*" OR "angiotensin-induc*" OR "anthracycline" OR "antiangiogenesis agents" OR "antibody-induced" OR "anti-DNA antibodies" OR "anti-mouse-GBM sera" OR "antineutrophil cytoplasmic autoantibody" OR "antiretroviral therapy" OR "anti-thymocyte serum" OR "anti-trinitrophenol switch variant mAbs" OR "AOPP-modified rat serum albumin" OR "apoferritin" OR "Aprotinin" OR "arachidonic acid" OR "areca nut chewing" OR "aristoloch*" OR "arsenic" OR "arsine gas" OR "Artemisia herba-alba" OR "asbestos" OR "Aspergillus" OR "aspirin" OR "asphalt" OR "AT1 receptor antagonist*" OR "atazanavir" OR "Atorvastatin" OR "ATRA" OR

"axitinib" OR "ayurvedic treatment*" OR "azathioprine" OR "azithromycin" OR "azobenzenearsonate" OR "bardoxolone methyl" OR "Barmah Forest virus" OR "Bartonella henselae" OR "bcl-induc*" OR "benoxaprofen" OR "beryllium" OR "beta-hemolysin/cytolysin" OR "beta-lactam" OR "betel nut chewing" OR "bevacizumab" OR "bezafibrate" OR "bile duct ligation" OR "binge eating-childhood" OR "bisacodyl" OR "bismuth" OR "bisphosphonate*" OR "bitumen" OR "bk-virus-induc*" OR "bleomycin" OR "blood lead" OR "bortezomib" OR "bovine serum albumin" OR "bromodichloromethane" OR "Bromocriptine mesylate" OR "bromoform" OR "bronchitis virus Cal99" OR "Brucella" OR "bucillamine" OR "bupivacaine" OR "Burkholderia pseudomallei" OR "burn injury" OR "Buspirone" OR "C1q" OR "Ca(2+)" OR "cadmium" OR "caffeine" OR "calcineurin inhibitor-induc*" OR "calcitriol-induced" OR "Campylobacter jejuni" OR "Candida albicans" OR "Candida tropicalis" OR "Candidemia" OR "cantharidin" OR "Capecitabine" OR "captopril" OR "carbon dioxide" OR "carrageenin" OR "carbamazepine" OR "Carbenoxolone" OR "carbon monoxide" OR "carbon tetrachloride" OR "carboplatin" OR "carmustine" OR "C-arylsuccinimides" OR "cecal ligation" OR "cediranib" OR "cefdinir" OR "Cefoxitin" OR "ceftriaxone" OR "Cefuroxime" OR "celecoxib" OR "cephaloridine" OR "cephalosporin*" OR "Ceramide" OR "cereal grains" OR "cetuximab" OR "childhood adversity" OR "chinese herb*" OR "chironomid larvae" OR "chitin" OR "Chlamydia pneumoniae" OR "chlorambucil" OR "chlorine" OR "chloroform" OR "chloroquine" OR "chlorpromazine" OR "chlorprothixene" OR "Chlorthalidone" OR "chlorpyrifos" OR "cholesterol-induced" OR "chromium" OR "ciclosporin" OR "cidofovir" OR "cigarette*" OR "cimetidine" OR "ciprofibrate" OR "ciprofloxacin" OR "cisplatin" OR "Citrobacter rodentium" OR "Clarithromycin" OR "classic heat stroke" OR "clometacin" OR "clomipramine" OR "clopidogrel" OR "Clostridium difficile toxin" OR "Cloxacillin" OR "Clozapine" OR "cm-induc*" OR "cni exposure" OR "cni-induced" OR "cocaine" OR "cola" OR "colchicine" OR "colistin" OR "complete adjuvant" OR "concanavalin A" OR "connective tissue growth factor*" OR "contrast-induced" OR "contrast medium-induced" OR "copper" OR "copper sulfate" OR "coronary artery bypass" OR "corosolic acid" OR "corticosteroid" OR "cortinarius" OR "Corynebacterium renale" OR "cow milk processing" OR "Coxsackie B4 virus" OR "Coxsackie B virus*" OR "coxsackie virus" OR "crf induced" OR "crude nephritogenoside" OR "csa-induced" OR "CTGF" OR "Cupressus funebris Endl" OR "cya-induced" OR "cyclic* stretch*" OR "cyclophosphamide" OR "Cycloserine" OR "cyclosporine" OR "Cylindrospermopsin" OR "Cytomegalovirus" OR "Cytosine arabinoside" OR "Dampness and moulds in workplace buildings" OR "daunomycin" OR "daunorubicin" OR "Deferasirox" OR "deferoxamine" OR "DEHP" OR "dehydration" OR "Demeclocycline" OR "Dengue fever" OR "dengue hemorrhagic fever" OR "deoxycorticosterone acetate-induced" OR "deoxycytidine" OR "deoxynivalenol" OR "depression" OR "desipramine" OR "dexamethasone" OR "dexfenfluramine" OR "Dextran" OR "dextrose-TPN" OR "di-2-ethylhexyl-phthalate" OR "diacetylbenzidine" OR "dibromochloromethane" OR "diclofenac" OR "diethylacetylurea" OR "diethylene glycol" OR "Diflunisal" OR "Digoxin" OR "diltiazem" OR "dimeglumine" OR "dimethylnitrosamine" OR "dinitrochlorobenzene" OR "dioxane" OR "dioxin*" OR "diphenylhydantoin" OR "diphosphonate*" OR "diphtheria toxin" OR "dipyrone" OR "Dirofilaria immitis" OR "Disopyramide" OR "doca-induced" OR "doca-salt" OR "domestic gas" OR "don expos*" OR "don-induced" OR "doxepin" OR "dox-induced" OR "doxorubicin" OR "doxycycline" OR "d-penicillamine" OR "dRK6" OR "dxr-induced" OR "Echinococcus" OR "e. coli-induc*" OR "Efavirenz" OR "effort-reward imbalance" OR "Ehrlichia canis" OR "elastase" OR "emc virus-induc*" OR "emotional abuse" OR "enoldopam" OR "enoxaparin" OR "Enterococcus faecalis" OR "epoetin-induced" OR "epo-induced" OR "epoxy compound*" OR "epstein-barr-virus-induc*" OR "Erythromycin" OR "erythropoietin-alpha" OR

"erythropoietin-induced" OR "escherichia coli-induc*" OR "esomeprazole" OR "etanercept" OR "Ethambutol" OR "ethanol" OR "ethionine" OR "Ethosuximide" OR "ethylene glycol" OR "Excessive endurance exercise training" OR "Exercise-induced" OR "expos* to lead" OR "exertional heat stroke" OR "exosome-like vesicles" OR "falciparum malaria" OR "Famotidine" OR "fangchi" OR "fenbufen" OR "Fenclofenac" OR "fenfluramine" OR "fenoldopam-induc*" OR "fenofibrate" OR "Fenoprofen" OR "Fentanyl citrate" OR "fiberglass" OR "fibrate therapy" OR "fibreglass" OR "firefighting activities" OR "flubiprofen" OR "flucloxacillin" OR "fluindione" OR "fluoro-10-methyl-1-2-benzanthracene" OR "fluoroquinolone*" OR "Fluoxetine" OR "fluphenazine" OR "flurbiprofen" OR "Flurithromycin" OR "folic acid-induc*" OR "formaldehyde" OR "formic acid" OR "Foscarnet" OR "free-fatty-acid-induced" OR "friend leukemia virus-induc*" OR "fructose" OR "fumonisin B1" OR "furantoin" OR "furosemide" OR "Fusarium graminearum" OR "fusidic acid" OR "gabapentin" OR "gadodiamide" OR "gadolinium" OR "gadopentetate dimeglumine" OR "Gemella haemolysans" OR "gasoline" OR "Gatifloxacin" OR "gbca exposure" OR "gcca exposure" OR "gd exposure" OR "gefitinib" OR "gemcitabine" OR "gemfibrozil" OR "gentamicin" OR "germanium" OR "germ-free" OR "Glucocorticoid" OR "glucosamine" OR "glucose-induc*" OR "glucose-peaks-short-term" OR "gluten" OR "glycerin" OR "glycerol-induc*" OR "gold" OR "grain dust" OR "GVHD" OR "haloperidol" OR "Hantaan virus" OR "Hantavirus" OR "hcy-induced" OR "heat stroke" OR "Helicobacter pylori" OR "heparin-induced" OR "hepatitis b-induced" OR "hepatitis b virus" OR "hepatitis c-induced" OR "hepatitis c virus" OR "hepatitis e-induced" OR "Hepatitis E virus" OR "hepatitis g-induced" OR "Hepatitis G virus" OR "heroin" OR "herpes simplex virus" OR "hetastarch" OR "hgcl2" OR "hg-induced" OR "high-fat-diet*" OR "high-glucose-induc*" OR High-glycemic-load diet*" OR "high home temperature" OR "high insulin" OR "high meat" OR "high-phosphate" OR "high-phosphorous-diet*" OR "high-protein-diet*" OR "high-protein-intake*" OR "high-protein-induc*" OR "high-salt-diet*" OR "high-salt-intake*" OR "high-saturated-fat diet*" OR "high selenium diet" OR "high-sodium-intake*" OR "high-sodium-diet*" OR "high-soybean oil" OR "high-sucrose-diet*" OR "high-tryptophan-diet*" OR "hiv-induced" OR "house dust mite" OR "human immunodeficiency virus" OR "human rhinovirus" OR "hyaluronidase" OR "hydralazine" OR "hydrocarbon*" OR "hydroxychloroquine" OR "hydrochlorothiazide" OR "hydroxyethylstarch" OR "hypothermia" OR "hypoxia-induc*" OR "ibuprofen" OR "ifosfamide" OR "IGF-1" OR "iloprost" OR "imipramine" OR "imiquimod" OR "Il-23" OR "Il-33" OR "indinavir" OR "Indomethacin" OR "indoxyl" OR "infliximab" OR "influenza A virus" OR "Influenza vaccination" OR "insulin-induced" OR "Insulin-like growth factor" OR "Interleukin-2" OR "interferon-alpha" OR "interferon-beta" OR "interferon-gamma" OR "interferon-induced" OR "Intracerebral hemorrhage" OR "intravenous immune globulin*" OR "intravenous immunoglobulin*" OR "iodin*" OR "iodixanol" OR "iohexol" OR "ionizing radiation" OR "iopamidol" OR "iron-induced" OR "iron-overload" OR "iron sucrose" OR "ischemia-induced" OR "isoniazid" OR "isoprenaline" OR "isopropyl alcohol" OR "Jatropha curcas phorbol ester*" OR "job strain" OR "jp4 gasoline" OR "Ketamine hydrochloride" OR "ketone*" OR "ketoprofen" OR "ketorolac" OR "Klebsiella pneumoniae" OR "lansoprazole" OR "lapatinib" OR "lassa virus" OR "laxative abuse" OR "lead burden" OR "lead exposure" OR "lead level*" OR "lead poisoning" OR "Leflunomide" OR "leprosy" OR "Leptospirosis" OR "levan" OR "levetiracetam" OR "Levofloxacin" OR "licorice" OR "lifetime psychological trauma exposure" OR "ligation of the renal parenchyma" OR "lilium" OR "lipid-induced" OR "lipopolysaccharide*" OR "lithium" OR "L-NAME-induced" OR "L-NNA" OR "long-term competitive strength exercise training" OR "lopinavir" OR "loratadine" OR "low fiber diet*" OR "low legumes intake" OR "low manganese intake" OR "low melatonin" OR "low potassium intake" OR "low pulses intake" OR "low shear stress" OR "low-Vitamin D

intake" OR "lps-induced" OR "lps-stimulated" OR "lymphocytic choriomeningitis virus" OR "maedi-visna virus" OR "magnolia officinalis" OR "malaria" OR "malathion" OR "maleic vinyl ether anhydride" OR "Maneb" OR "mannitol" OR "maprotiline" OR "measles virus" OR "meat" OR "mechanical strain" OR "mechanical stretch" OR "mechanical ventilation" OR "Mefanamic acid" OR "melamine" OR "menadione sodium bisulfite" OR "mercuric chloride" OR "mercury" OR "meropenem" OR "mesalamine" OR "mesalazine" OR "metformin" OR "methicillin" OR "Methocarbomol" OR "methotrexate" OR "methotrimeprazine" OR "methoxyflurane" OR "methyldopa" OR "methylene chloride" OR "methyl tertiary-butyl ether" OR "methylglyoxal" OR "Methylphenidate" OR "Methysergide" OR "metolazone" OR "Metoprolol" OR "mg-induced" OR "microRNA-induced" OR "midecamycin acetate" OR "minocycline" OR "mirtazapine" OR "mitomycin" OR "monocrotaline" OR "monosodium urate crystal" OR "morphine" OR "mothball abuse" OR "moxifloxacin" OR "MPP" OR "mtbe" OR "M-tropic SIVmacR71-17E" OR "mumps virus" OR "mushrooms" OR "mustard gas" OR "mu tong" OR "muzolimine" OR "N-3-5-dichlorophenyl-succinimide" OR "Na(+)" OR "nafcillin" OR "naproxen" OR "N-arylsuccinimides" OR "nasal decongestant*" OR "nelfinavir" OR "nematode" OR "Neomycin" OR "nickel" OR "nicotine" OR "Nifedipine" OR "niflumic acid" OR "nimesulide" OR "nitrendipine" OR "nitrofurantoin" OR "nitrogen mustard" OR "nitrogen oxides" OR "nivalenol" OR "n-methyl-n 1-nitro-n-nitroso guanidine" OR "n-n-diacetylbenzidine" OR "noise" OR "Nomifensine" OR "Non-esterified fatty acids" OR "nonsteroidal anti-inflammatory drug*" OR "non-steroidal anti-inflammatory drug*" OR "nonylphenol" OR "norepinephrine" OR "Norfloxacin" OR "nortriptyline" OR "NSAID*" OR "NVP-BKM120" OR "ochratoxin*" OR "O-glycosylated IgA rheumatoid factor" OR "olanzapine" OR "oleic acid" OR "olsalazine" OR "omega-6" OR "omeprazole" OR "oral-poliovirus vaccine" OR "organic solvent*" OR "orlistat" OR "ovalbumin" OR "oxalate" OR "oxidant-induced" OR "oxaliplatin" OR "oxytetracycline" OR "palmitate" OR "palmitic acid" OR "pamidronate" OR "p-Aminophenol" OR "pan-induced" OR "panitumumab" OR "pantoprazole" OR "papaverine-induced" OR "paracetamol" OR "paraphenylenediamine" OR "paraquat" OR "parental hypertension" OR "parental sucrose" OR "paroxetine" OR "particulate matter/ozone" OR "Parvovirus B19" OR "p-Cresyl sulfate" OR "pcr-rflp" OR "PDGF-BB" OR "pefloxacin" OR "penicillamine" OR "Penicillin*" OR "Penicillium aurantiogriseum" OR "pentachlorophenol" OR "Pentamidine" OR "pentazocine" OR "perchloroethylene" OR "perfluoroalkyl" OR "perfluorooctanoic acid" OR "pesticide*" OR "phenacetin" OR "Phenindione" OR "Phenobarbital" OR "phenol" OR "phenytoin" OR "Phenylbutazone" OR "phenylenediamine*" OR "Phenylephrine" OR "phenylpropanolamine" OR "phosphate*" OR "phosphatidylinositol-3-kinase inhibitor*" OR "phosphorus additive*" OR "physical inactivity" OR "Physostigmine" OR "pimozide" OR "Piperacillin" OR "piroxicam" OR "pirprofen" OR "Plasmodium brasilianum" OR "platinum" OR "Pleural Tuberculosis" OR "poliomyelitis vaccine" OR "polymyxin B" OR "polymethyl methacrylate" OR "Polyomavirus*" OR "porcine circovirus*" OR "porcine parvovirus*" OR "portosystemic shunt surgery" OR "pranlukast" OR "prednisolone" OR "prenatal hypoxia" OR "pressure-induced" OR "pressure overload" OR "pristane" OR "procainamide" OR "Prochlorperazine" OR "Propionibacterium acnes" OR "propoxyphene" OR "propylthiouracil" OR "Proton pump inhibitor*" OR "Probenecid" OR "protamine" OR "Proteus mirabilis" OR "prulifloxacin" OR "Pseudoephedrine hydrochloride" OR "Pseudomonas aeruginosa" OR "psychogenic polydipsia" OR "ptu-induc*" OR "pufferfish" OR "puromycin" OR "puumala virus*" OR "p-xylene" OR "Quercus calliprinos" OR "quetiapine" OR "Quinacrine" OR "Quinidine" OR "quinine" OR "quinolone" OR "rabeprazol" OR "radiation-induc*" OR "radiocontrast-induced" OR "Ranitidine" OR "rapamycin" OR "refined cereals" OR "reperfusion-induced" OR "residential remoteness" OR

"respiratory syncytial virus" OR "Respiratory tract virus*" OR "retinoic acid-induced" OR "rhuepo-induced" OR "rifampicin" OR "rifampin" OR "risperidone" OR "Ritodrine hydrochloride" OR "ritonavir" OR "rofecoxib" OR "Ross River virus*" OR "Rubella virus*" OR "salt-induced" OR "salmonella" OR "scarlet pimpernel" OR "Schistosoma haematobium" OR "Schistosoma mansoni" OR "Scopolamine" OR "sedentary" OR "Selegiline" OR "Selenium deficiency soil" OR "Sendai virus" OR "Serratia marcescens" OR "serotonin" OR "short sleep duration" OR "silane" OR "silica" OR "silicon dioxide" OR "silicosis" OR "silver" OR "sitting time" OR "sleep deprivation" OR "smoking" OR "snakebite*" OR "snake venom" OR "social environment" OR "sodium additives" OR "sodium barbital" OR "sodium valproate" OR "sorafenib" OR "soybean oil heated repeatedly" OR "soy-rich diet" OR "spirapril" OR "spironolactone" OR "Staphylococcus aureus"OR "star fruit" OR "statins" OR "St. John's Wort" OR "steroid-induced" OR "streptococcal pyrogenic exotoxin B" OR "Streptococcus agalactiae" OR "Streptococcus mutans" OR "streptomycin" OR "streptozocin-induced" OR "streptozotocin-induced" OR "stress-induced" OR "styrene" OR "stz-induced" OR "stz-treated" OR "sulfadiazine" OR "Sulfasalazine" OR "sulindac" OR "sulfonylurea*" OR "sulfur dioxide" OR "Sulindac" OR "sulphasalazine" OR "Sulphinpyrazone" OR "sulpiride" OR "sunflower oil" OR "sunitinib" OR "superdrol" OR "surgically-induced" OR "swine fever virus*" OR "tacrolimus" OR "Tamm-Horsfall protein" OR "tazobactam" OR "TcdA" OR "TcdB" OR "TCDD" OR "Telazol" OR "Telithromycin" OR "tenofovir" OR "testosterone" OR "tetrachlorodibenzo-p-dioxin" OR "tetrachloroethylene" OR "Tetracycline*" OR "tetrandrine" OR "tetramethylbenzidine" OR "tetrodotoxin" OR "TGF-beta" OR "Thiazides" OR "Thioridazine hydrochloride" OR "thrombolytic therapy" OR "Thy-1.1 monoclonal antibody" OR "ticlopidine" OR "tiletamine" OR "tiopronin" OR "tissue kallikrein antibody" OR "titanium dioxide nanoparticles" OR "tobacco" OR "Tobramicin" OR "Tolmetin" OR "toluene" OR "total parenteral nutrition-overfeeding infants" OR "Toxocara canis" OR "TPA" OR "transmitted transfusion virus*" OR "traumatic brain injury" OR "Triamterene" OR "trichloroethane" OR "trichloroethylene" OR "trihalomethane" OR "triiodobenzoic acid*" OR "trimethadione" OR "trimethoprim-sulfamethoxazole" OR "trimethylpentane" OR "trimipramine" OR "tripelennamine" OR "Trypanosoma brucei" OR "U1-70-kd small nuclear ribonucleoprotein" OR "ureteropelvic junction stenosis" OR "ureteral obstruction" OR "uranium" OR "uranyl nitrate" OR "UVB" OR "vacor" OR "valdecoxib" OR "valproic acid" OR "valpromide" OR "varicella-zoster virus" OR "vancomycin" OR "vegf-inhibit*" OR "Venlafaxine" OR "ventilator-induced" OR "verapamil" OR "verbesina encelioides" OR "verteporfin" OR "vinyl isolator breeding" OR "vomitoxin" OR "vt-induced" OR "warfarin" OR "west nile virus" OR "wheat" OR "whole-body irradiation" OR "wortmannin" OR "Yersinia pseudotuberculosis" OR "Yohimbine hydrochloride" OR "zinc-deficient diet-maternal" OR "zinc-phosphide" OR "zolendronate" OR "Zopiclone")

OR

1b. MESH HEADINGS

("kidney failure, chronic" OR "renal insufficiency, chronic" OR "Diabetic Nephropathies" OR Nephrosclerosis OR Nephrosis OR Nephritis OR "Nephritis, Interstitial")

OR

1c. TOPIC PHRASES

"Chronic Kidney Disease"

AND

2. **TITLE PHRASES**

((Amiodarone OR Antipsychotic* OR "anti-infective*" OR antiadrenergic OR antiandrogen* OR antianginal OR antiarrhythmic OR antiasthmatic OR antibiotic* OR antineoplastic* OR antiemetic* OR anticholinergic* OR antispasmodic* OR anticoagulant* OR anticonvulsant* OR antidepressant* OR antidiarrheal* OR antiemetic OR antivertigo OR antifungal* OR antigonadotropic OR antigout OR antihistamine* OR antimalarial OR antimetabolite* OR antimigraine OR antiparkinson OR antiplatelet OR antipseudomonal OR antipsoriatic* OR antirheumatic* OR antiseptic OR germicide* OR antitoxin* OR antivenin* OR antituberculosis OR antitussive* OR antiviral OR Azole* OR Barbiturate* OR Bleomycin OR "Calcium Channel Blocker" OR Chloramphenicol OR Chlorpromazine OR Digitalis OR Haloperidol OR Halothane OR Ketoconazole OR Metronidazole OR Niacin OR Nitroglycerin OR Primaquine OR Sulfonamide* OR Tamoxifen OR Thioridazine OR Tricyclics OR "Valproic Acid") near/1 (caus* OR induc*)) OR ("*toxic" OR "*toxici*" OR "toxicologic*" OR "toxica*" OR "poison*" OR contamina* OR "adverse* effect*" OR "side effect*" OR "deleterious effect*" OR "negative effect*" OR "detrimental effect*" OR diet* near/1 effect* OR "ecotoxologic* effect*" OR particulate* near/1 effect* OR "adverse reaction*" OR "adverse food" OR "adverse drug" OR "adverse health" OR "expos*" OR "additives" OR "chemicals" OR "abuse*" OR "harm" OR "harms" OR "harmful" OR "aggravate*" OR "occupation*" OR "intoxicat*" OR pollut* OR "*virus*" OR antibiotic* OR environmental OR drug*-induc* OR chemotherapy-induc* OR treat*-induc* OR stress-induc* OR chemical*-induc* OR cytokine*-induc* OR exercise-induc* OR surg*-induc* OR diet*-induc* OR radiation-induc* OR steroid-induc* OR mechanically-induc* OR "damage-induc*" OR "damage-caus*" OR drug*-caus* OR chemotherapy-caus* OR treat*-caus* OR stress-caus* OR chemical*-caus* OR cytokine*-caus* OR exercise-caus* OR surg*-caus* OR diet*-caus* OR radiation-caus* OR steroid-caus* OR mechanically-caus* OR *OBACTER OR Chlamydia OR Chlamydophila OR Clostridium OR *Bacterium OR *Chia OR *Ococcus OR Haemophilus OR Mycoplasma OR Neisseria OR *Omonas OR Rickettsia OR Rochalimaea OR marcescens OR Treponema OR Vibrio OR Yersinia OR *benzene OR trichloro* OR hexachloro* OR dichloro* OR tetrachloro* OR parachloro* OR dinitro* OR pentachloro* OR polychlor* OR *phthalate OR *ethane OR *toluene OR *nitrophenol* OR perfluor* OR polyfluor* OR polybrom* OR hexabrom* OR decabrom* OR tetrabrom* OR waterborne OR "water-borne" OR dietborne OR "sediment-associated" OR "particle-associated" OR "traffic-related" OR "work-related") OR (((caus* OR induc*) near/5 (hypertension)) NOT ("hypertension caus*" OR "caused by hypertension" OR "hypertension induc*" OR "induced by hypertension")) OR ("hypertension was due to" OR "hypertension due to" OR "lead* to hypertension" OR "result* in hypertension" OR "role in hypertension" OR "hypertension was produced by" OR "hypertension produced by" OR "associated with hypertension" OR "hypertension was associated with" OR "association of hypertension" OR "association between hypertension" OR "mediate* hypertension" OR "hypertension mediated by" OR "hypertension was mediated by" OR "role in hypertension" OR "hypertension provoked by" OR "hypertension was provoked by" OR "provoked hypertension" OR "produce* hypertension" OR "hypertension was produced by" OR "risk* of hypertension" OR "risk* for hypertension" OR "hypertension risk factor*" OR "involvement in hypertension" OR "incidence of hypertension" OR "incident hypertension" OR "getting hypertension" OR "prevalence of hypertension" OR "susceptib* to hypertension" OR "contribut* to hypertension" OR "related to hypertension" OR "relationship between hypertension" OR "relationship

with hypertension" OR "development of hypertension" OR "develop* hypertension" OR "aggravat* hypertension" OR "resulted in hypertension")

3. MESH QUALIFIERS - MESH HEADING

(/"chemically induced" OR /toxicity OR /poisoning)

OR

4. MESH GENERIC TERMS - MESH HEADING NO EXPLODE

Abnormalities, Drug-Induced OR Air Pollutants, Occupational OR Anti-Allergic Agents/adverse effects OR Anti-Asthmatic Agents/adverse effects OR Antibiotics, Antitubercular/adverse effects OR Anticonvulsants/adverse effects OR Antidepressive Agents/adverse effects OR Anti-Infective Agents/adverse effects OR Anti-Infective Agents, Urinary/adverse effects OR Antimanic Agents/adverse effects OR Antineoplastic Agents/adverse effects OR Antipsychotic Agents/adverse effects OR Antipyretics/adverse effects OR Antirheumatic Agents/adverse effects OR Antithyroid Agents/adverse effects OR Antitubercular Agents/adverse effects OR Anti-Ulcer Agents/toxicity OR Anti-Allergic Agents/toxicity OR Anti-Asthmatic Agents/toxicity OR Antibiotics, Antitubercular/toxicity OR Anticonvulsants/toxicity OR Antidepressive Agents/toxicity OR Anti-Infective Agents/toxicity OR Anti-Infective Agents, Urinary/toxicity OR Antimanic Agents/toxicity OR Antineoplastic Agents/toxicity OR Antipsychotic Agents/toxicity OR Antipyretics/toxicity OR Antirheumatic Agents/toxicity OR Antithyroid Agents/toxicity OR Antitubercular Agents/toxicity OR Anti-Ulcer Agents/toxicity OR Congenital Abnormalities OR Congenital Disorders of Glycosylation OR Dermatitis, Occupational OR Drug Eruptions OR Drug Hypersensitivity OR Drug Toxicity OR Environmental Exposure OR Environmental Illness OR Environmental Monitoring OR Environmental Pollutants OR Fast Foods OR Food Additives OR Food Contamination OR Food Habits OR Food Preservatives OR Fossil Fuels OR Glycosylation End Products, Advanced OR Hallucinogens OR Hazardous Substances OR Herbicides OR Household Products OR Hydrocarbons OR Hydrocarbons, Alicyclic OR Hydrocarbons, Aromatic OR Hydrocarbons, Chlorinated OR Hydrocarbons, Fluorinated OR Hydrocarbons, Halogenated OR Iatrogenic Disease OR Inhalation Exposure OR Insecticides OR Leisure Activities OR Marine Toxins OR Maternal Exposure OR Mutagens OR Mycotoxins OR Neurotoxins OR Nonprescription Drugs OR Occupational Diseases OR Occupational Exposure OR Occupations OR Organic Chemicals OR Paternal Exposure OR Pesticides OR Plant Poisoning OR Plants, Toxic OR Poisoning OR Poisons OR Prenatal Exposure Delayed Effects OR Soil Pollutants OR Solvents OR Substance-Related Disorders OR Sweetening Agents OR Vehicle Emissions OR Water Pollutants, Chemical OR Welding

1C. CKD Treatments

In parallel to the causes query structure ([Cause][Produces][Symptom]), we will define a treatments query structure. An initial candidate is: ([Treatment][Eliminates][Symptom]). Various combinations of Treatment/Eliminates/Symptom may be used (e.g., Treatment near Symptom, Eliminates near Symptom, Treatment near Eliminates, etc), and all will provide complementary retrievals, with some degree of overlap.

Treatment query examples.

1. Treatment near Eliminates: sulforaphane near/5 eliminated; steroid near/5 reduced; diet near/5 improved: antibiotic near/1 reduced.

2. Eliminates near Symptom: reduce* near/5 hypertension NOT hypertension reduce*

3. Treatment near Symptom: sulforaphane in title, with either Symptom in title or MeSH. If we go to Abstracts, we need stronger proximity condition; i.e., sulforaphane near/5 hypertension. Unlike case 1, in this case the treatments are specific members of classes of potential treatments that usually have beneficial effects, and therefore don't require proximity to treatment-like terms; the treatment nature is implied by the substance. Adding a proximity condition gives higher Precision at the expense of Recall.

1C1. CKD core literature treatments

Query=(#1 NOT (#1a OR #1b OR #1c OR #1d)) AND ((2a NOT 2b) OR 2c OR 3a OR (4b AND 4c))

1. **TOTAL CKD RETRIEVAL**

1a. ("kidney failure, chronic" OR "renal insufficiency, chronic" OR "Diabetic Nephropathies" OR Nephrosclerosis OR Nephrosis OR Nephritis OR "Nephritis, Interstitial") - **MeSH Heading**

OR

1b. "chronic kidney disease" - **topic**

NOT

1c. (Renal Dialysis OR Kidney Transplantation OR Peritoneal Dialysis OR Peritoneal Dialysis, Continuous Ambulatory OR Nephrectomy OR Transplantation, Homologous OR Graft Rejection OR Graft Survival OR Dialysis Solutions OR Dialysis OR Hemodialysis, Home OR Hemodialysis Solutions OR Hemodialysis Units, Hospital OR Microdialysis OR Transplantation, Autologous OR Transplantation Immunology OR Transplantation Conditioning OR Transplantation, Heterologous OR Delayed Graft Function OR Kidney Neoplasms OR Renal Replacement Therapy OR Pancreas Transplant OR Neoplasms) - MeSH Heading Field

(NEGATION TERMS FROM INITIAL CKD CORE TREATMENTS IDENTIFICATION)

NOT

1d. ("22-oxacalcitriol" OR "acetaminophen" OR "acetylcysteine" OR "Acetylsalicylic Acid" OR "theophylline" OR "ADP P2Y(12) antagonist*" OR "aerobic exercise" OR "aldosterone antagonist*" OR

"aldosterone receptor antagonist*" OR "alfacalcidol" OR "aliskiren" OR "alkylating agent*" OR "allogeneic" OR "Allopurinol" OR "alpha-galactosidase" OR "alpha-glucosidase inhibitor*" OR "aluminum" OR "amlodipine" OR "amphotericin" OR "analgesic" OR "androgen" OR "angiotensin II antagonist*" OR "angiotensin II receptor antagonist*" OR "angiotensin-converting-enzyme-inhibitor*" OR "angiotensin-receptor blocker*" OR "antiplatelet therapy" OR "apocynin two inhibitor*" OR "aranesp" OR "artery bypass" OR "artery revascularization" OR "artery stenting" OR "ascorbic acid" OR "Aspirin" OR "AST-120" OR "Astragalus" OR "asymmetric dimethylarginine" OR "AT1 receptor antagonist*" OR "atenolol" OR "Atorvastatin" OR "AVE7688" OR "Azathioprine" OR "azelnidipine" OR "balloon angioplasty" OR "benazepril" OR "benidipine" OR "beta-adrenergic receptor antagonist*" OR "beta-blocker*" OR "Bifidobacteri*" OR "bisphosphonate*" OR "Bivalirudin" OR "blood transfusions" OR "BMP-7" OR "bone marrow transplantation" OR "bone morphogenetic protein-7" OR "bosentan" OR "BQ-123" OR "B-type natriuretic peptide*" OR "calcification inhibitor*" OR "calcineurin inhibitor*" OR "calcitonin" OR "calcitriol" OR "calcium acetate" OR "calcium antagonist*" OR "calcium carbonate" OR "calcium channel blocker*" OR "calcium supplementation" OR "candesartan" OR "captopril" OR "carnitine" OR "carvedilol" OR "Cell therapy" OR "cephalosporin*" OR "cereal" OR "charcoal" OR "chemotherap*" OR "Chinese herbs" OR "Chlorthalidone" OR "cholecalciferol" OR "cilazapril" OR "cinacalcet" OR "Clarithromycin" OR "clonidine" OR "clopidogrel" OR "coenzyme A reductase inhibitor*" OR "competitive methyltransferase inhibitor*" OR "coronary revascularization" OR "corticosteroid*" OR "COX-2 inhibitor*" OR "CS-866" OR "curcumin" OR "Cyclophosphamide" OR "cyclosporine" OR "CYP24A1 inhibitor*" OR "CYP3A4 inhibitor*" OR "dairy product*" OR "darbepoetin" OR "darbepoetin alfa" OR "darbepoetin alpha" OR "DES implantation" OR "dexamethasone" OR "dietary fiber" OR "dietary phosphate restriction" OR "dietary soy" OR "digoxin" OR "dihydropyridine" OR "diltiazem" OR "dipeptidyl peptidase-4 inhibitor*" OR "diphenylene iodinium" OR "diphosphate ADP P2Y(12) antagonist*" OR "direct renin inhibitor*" OR "direct thrombin inhibitor*" OR "dobutamine" OR "dopamine" OR "doxercalciferol" OR "doxorubicin" OR "Doxycycline" OR "DPP-4 inhibitor*" OR "enalapril" OR "endothelin A receptor antagonist*" OR "endothelin receptor antagonist*" OR "endovascular therapy" OR "enoxaparin" OR "epinephrine" OR "eplerenone" OR "epoetin" OR "epoetin alfa" OR "epoetin beta" OR "Eprex" OR "ergocalciferol" OR "erythropoiesis-stimulating agent*" OR "Erythropoietic agent*" OR "erythropoietin" OR "essential amino acid*" OR "estradiol" OR "estrogen" OR "ET(A) receptor antagonist*" OR "ethanol" OR "everolimus" OR "ezetimibe" OR "factor-alpha plasminogen activator inhibitor-1" OR "felodipine" OR "Fenofibrate" OR "ferric carboxymaltose" OR "ferric gluconate" OR "Ferumoxytol" OR "fetuin-A" OR "FISH" OR "fish oil" OR "flaxseed" OR "fluvastatin" OR "folic acid" OR "fondaparinux" OR "furosemide" OR "garlic" OR "GBCA" OR "gene therapy" OR "gene transfer" OR "Ghrelin" OR "glucocorticoid" OR "glycoprotein IIb/IIIa inhibitor*" OR "growth hormone" OR "GW9662" OR "H2-blocker*" OR "H2-receptor antagonist*" OR "Hematide" OR "heparin*" OR "hepatocyte growth factor" OR "hepcidin" OR "herb" OR "herbal medicine" OR "HMG-CoA reductase inhibitor*" OR "HOE 140" OR "hormone replacement therapy" OR "human growth hormone" OR "hydralazine" OR "hydration" OR "hydrochlorothiazide" OR "hydroxymethylglutaryl-CoA reductase inhibitor*" OR "hypoglycemic agent*" OR "IGF-1" OR "IL-1Ra" OR "imatinib" OR "immunosuppression" OR "immunosuppressive agent*" OR "indinavir" OR "inhibitor of metalloproteinase-1" OR "Inhibitors of NADPH oxidase" OR "insulin therapy" OR "insulin-like growth factor*" OR "interferon" OR "Interleukin-1 receptor antagonist*" OR "intravenous iron" OR "Irbesartan" OR "Irbesartan" OR "iron dextran" OR "iron sucrose" OR "iron supplementation" OR "iron therapy" OR "isoflavone" OR "ketoacids" OR "kinase

inhibitor p21" OR "Kremezin" OR "lanthanum" OR "l-arginine" OR "lercanidipine" OR "linezolid" OR "lipid-lowering agent*" OR "lipid-lowering drug*" OR "lisinopril" OR "lisinopril" OR "loop diuretics" OR "losartan" OR "low molecular weight heparin" OR "low-protein diet" OR "LU 135252" OR "Magnesium" OR "maxacalcitol" OR "medoxomil" OR "melanocortin-4 receptor antagonist*" OR "mesenchymal stem cell*" OR "Metformin" OR "methylprednisolone" OR "Metoprolol" OR "MG132" OR "mineralocorticoid receptor antagonist*" OR "Mineralocorticoid receptor block*" OR "mycophenolate mofetil" OR "myostatin inhibition" OR "N-acetylcysteine" OR "Nebivolol" OR "NESP" OR "nifedipine" OR "nitric oxide synthase inhibitor*" OR "non-dihydropyridine calcium antagonist*" OR "non-dihydropyridine calcium channel blocker*" OR "Nonsteroidal anti-inflammatory drugs" OR "Non-steroidal anti-inflammatory drugs" OR "Nutritional therapy" OR "Olmesartan" OR "omega-3 fatty" OR "omeprazole" OR "opioid antagonist*" OR "opioid receptor antagonist*" OR "Opioids" OR "P2Y(12) receptor antagonist*" OR "pamidronate" OR "paracetamol" OR "paricalcitol" OR "pentoxifylline" OR "peptidase-4 inhibitor*" OR "percutaneous ethanol injection" OR "percutaneous transluminal renal angioplasty" OR "perindopril" OR "Peroxisome proliferator-activated receptor" OR "phenacetin" OR "phosphate binder*" OR "phosphodiesterase inhibitor*" OR "phosphodiesterase-5 inhibitor*" OR "phosphorus binder*" OR "phosphorus restriction*" OR "phototherapy" OR "physical exercise" OR "phytochemical*" OR "Phytoestrogens" OR "phyto-oestrogens" OR "pioglitazone" OR "Pitavastatin" OR "plasminogen activator inhibitor*" OR "polymerase inhibitor*" OR "polyunsaturated fatty acid*" OR "PPAR-gamma antagonist*" OR "pravastatin" OR "prednisolone" OR "prednisone" OR "protease inhibitor*" OR "protein restriction" OR "proton pump inhibitor*" OR "PTRA" OR "Ptx" OR "pulse therapy" OR "Pyrophosphate" OR "pyrrolidine-dithiocarbamate" OR "pyrrolidine-dithiocarbamate" OR "quinapril" OR "R-568" OR "ramipril" OR "Rapamycin" OR "Recombinant human erythropoietin" OR "reductase inhibitor*" OR "renal revascularization" OR "renin inhibitor*" OR "renin-angiotensin system block*" OR "restenosis" OR "reverse transcriptase inhibitor*" OR "rhEPO" OR "rHuEPO" OR "ribavirin" OR "ritanserin" OR "rituximab" OR "rosiglitazone" OR "rosuvastatin" OR "rottlerin" OR "ruboxistaurin" OR "salt restriction" OR "selective serotonin reuptake inhibitor*" OR "sevelamer" OR "sildenafil" OR "sildenafil" OR "simvastatin" OR "smoking cessation" OR "SMP-534" OR "sodium bicarbonate" OR "sodium restriction" OR "sodium thiosulfate" OR "somatostatin" OR "Soy protein*" OR "spironolactone" OR "src inhibitor*" OR "statin therapy" OR "statin treatment" OR "stent implantation" OR "surgical revascularization" OR "telmisartan" OR "temocapril" OR "Tempol" OR "Tenofovir" OR "Testosterone" OR "TFPI" OR "thiazide" OR "Thiazolidinediones" OR "thrombin inhibitor*" OR "thrombomodulin" OR "tissue engineering" OR "tolvaptan" OR "TRAM-34" OR "Trandolapril" OR "transluminal angioplasty" OR "type 1 receptor blocker*" OR "tyrosine kinase inhibitor*" OR "U-0126" OR "unfractionated heparin" OR "uricosuric agent*" OR "V2 receptor antagonist*" OR "valsartan" OR "vascular endothelial growth factor" OR "vasopeptidase inhibitor*" OR "vasopressin receptor antagonist*" OR "vasopressin V2 receptor antagonist*" OR "VDR activator*" OR "VDRA" OR "vegetable protein*" OR "VEGF" OR "verapamil" OR "vessel revascularization" OR "vitamin B12" OR "vitamin C" OR "vitamin D" OR "vitamin D receptor activator*" OR "vitamin E" OR "Vitamin K" OR "vitamin K antagonists" OR "VKA" OR "anticoagulation therapy" OR "warfarin" OR "xanthine oxidase inhibitor*" OR "Zinc") - title

AND

2. **TITLE PHRASES - (excludes dialysis or transplants)**

2a. ((*treat* OR *therap* OR cure* OR intervention* OR rehabilitat* OR medication* OR drug* OR stimulant* OR pharmacological* OR diet* OR supplementation OR renoprotect* OR nephroprotect* OR "prevent* progressi*" OR "retard* the progressi*" OR "delay* the progressi*" OR "reduc* the progressi*" OR "attenuat* the progressi*" OR "halt* the progressi*" OR "inhibit* the progressi*" OR "suppress* the progressi*" OR "alleviat* the progressi" OR "oppos* the progressi" OR "imped* the progressi*" OR "limit* the progressi*" OR "ameliorat* the progressi*" OR protect* OR alleviate* OR ameliorate* OR improv* OR benefit*) OR ((reduc* OR inhibit* OR decreas* OR prevent* OR suppress* OR lessen* OR lower* OR mitigat*) near/1 (glycat* OR "peripheral vascular disease" OR arteriosclerosis OR vasoconstriction OR glycosylat* OR endothelin-1 OR inflammation OR hypertension OR "insulin resistance" OR fibrosis OR "metabolic syndrome" OR hyperglycemia OR nephropathy OR fibrogenesis OR "arterial stiffness" OR "renal injury" OR "renal damage" OR "renal failure" OR "renal insufficiency" OR "renal disease" OR "kidney injury" OR "kidney damage" OR "kidney failure" OR "kidney disease"))) - title

(the above is the 'reduce' option, where reduction of effects is desired. If an increase is desired, the appropriate 'increase' terminology is substituted for the 'reduce' terminology above)

NOT

2b. (glycat*-reduc* OR glycat*-inhibit* OR glycat*-decreas* OR glycat*-prevent* OR glycat*-suppress* OR glycat*-lessen* OR glycat*-lower* OR glycat*-mitigat* OR "glycat* caus*" OR "caused by glycat*" OR "glycat* induc*" OR "induced by glycat*" OR "glycat* was due to" OR "glycat* due to" OR "lead* to glycat*" OR "result* in glycat*" OR "role in glycat*" OR "glycat* was produced by" OR "glycat* produced by" OR "role in glycat*" OR "glycat* provoked by" OR "glycat* was provoked by" OR "provoked glycat*" OR "produce* glycat*" OR "glycat* was produced by" OR "incidence of glycat*" OR "incident glycat*" OR "getting glycat*" OR "prevalence of glycat*" OR "susceptib* to glycat*" OR "contribut* to glycat*" OR "development of glycat*" OR "develop* glycat*" OR "aggravat* glycat*" OR "resulted in glycat*") OR ("peripheral vascular disease reduc*" OR "peripheral vascular disease inhibit*" OR "peripheral vascular disease decreas*" OR "peripheral vascular disease prevent*" OR "peripheral vascular disease suppress*" OR "peripheral vascular disease lessen*" OR "peripheral vascular disease lower*" OR "peripheral vascular disease mitigat*" OR "peripheral vascular disease caus*" OR "caused by peripheral vascular disease" OR "peripheral vascular disease induc*" OR "induced by peripheral vascular disease" OR "peripheral vascular disease was due to" OR "peripheral vascular disease due to" OR "lead* to peripheral vascular disease" OR "result* in peripheral vascular disease" OR "role in peripheral vascular disease" OR "peripheral vascular disease was produced by" OR "peripheral vascular disease produced by" OR "role in peripheral vascular disease" OR "peripheral vascular disease provoked by" OR "peripheral vascular disease was provoked by" OR "provoked peripheral vascular disease" OR "produce* peripheral vascular disease" OR "peripheral vascular disease was produced by" OR "incidence of peripheral vascular disease" OR "incident peripheral vascular disease" OR "getting peripheral vascular disease" OR "prevalence of peripheral vascular disease" OR "susceptib* to peripheral vascular disease" OR "contribut* to peripheral vascular disease" OR "development of peripheral vascular disease" OR "develop* peripheral vascular disease" OR "aggravat* peripheral vascular disease" OR "resulted in peripheral vascular disease") OR (arteriosclerosis-reduc* OR arteriosclerosis-inhibit* OR arteriosclerosis-decreas* OR arteriosclerosis-prevent* OR arteriosclerosis-suppress* OR arteriosclerosis-lessen* OR arteriosclerosis-lower* OR arteriosclerosis-mitigat* OR "arteriosclerosis caus*" OR "caused by arteriosclerosis" OR "arteriosclerosis induc*" OR "induced by arteriosclerosis" OR "arteriosclerosis was

due to" OR "arteriosclerosis due to" OR "lead* to arteriosclerosis" OR "result* in arteriosclerosis" OR "role in arteriosclerosis" OR "arteriosclerosis was produced by" OR "arteriosclerosis produced by" OR "role in arteriosclerosis" OR "arteriosclerosis provoked by" OR "arteriosclerosis was provoked by" OR "provoked arteriosclerosis" OR "produce* arteriosclerosis" OR "arteriosclerosis was produced by" OR "incidence of arteriosclerosis" OR "incident arteriosclerosis" OR "getting arteriosclerosis" OR "prevalence of arteriosclerosis" OR "susceptib* to arteriosclerosis" OR "contribut* to arteriosclerosis" OR "development of arteriosclerosis" OR "develop* arteriosclerosis" OR "aggravat* arteriosclerosis" OR "resulted in arteriosclerosis")

OR

(vasoconstriction-reduc* OR vasoconstriction-inhibit* OR vasoconstriction-decreas* OR vasoconstriction-prevent* OR vasoconstriction-suppress* OR vasoconstriction-lessen* OR vasoconstriction-lower* OR vasoconstriction-mitigat* OR "vasoconstriction caus*" OR "caused by vasoconstriction" OR "vasoconstriction induc*" OR "induced by vasoconstriction" OR "vasoconstriction was due to" OR "vasoconstriction due to" OR "lead* to vasoconstriction" OR "result* in vasoconstriction" OR "role in vasoconstriction" OR "vasoconstriction was produced by" OR "vasoconstriction produced by" OR "role in vasoconstriction" OR "vasoconstriction provoked by" OR "vasoconstriction was provoked by" OR "provoked vasoconstriction" OR "produce* vasoconstriction" OR "vasoconstriction was produced by" OR "incidence of vasoconstriction" OR "incident vasoconstriction" OR "getting vasoconstriction" OR "prevalence of vasoconstriction" OR "susceptib* to vasoconstriction" OR "contribut* to vasoconstriction" OR "development of vasoconstriction" OR "develop* vasoconstriction" OR "aggravat* vasoconstriction" OR "resulted in vasoconstriction") OR (glycosylat*-reduc* OR glycosylat*-inhibit* OR glycosylat*-decreas* OR glycosylat*-prevent* OR glycosylat*-suppress* OR glycosylat*-lessen* OR glycosylat*-lower* OR glycosylat*-mitigat* OR "glycosylat* caus*" OR "caused by glycosylat*" OR "glycosylat* induc*" OR "induced by glycosylat*" OR "glycosylat* was due to" OR "glycosylat* due to" OR "lead* to glycosylat*" OR "result* in glycosylat*" OR "role in glycosylat*" OR "glycosylat* was produced by" OR "glycosylat* produced by" OR "role in glycosylat*" OR "glycosylat* provoked by" OR "glycosylat* was provoked by" OR "provoked glycosylat*" OR "produce* glycosylat*" OR "glycosylat* was produced by" OR "incidence of glycosylat*" OR "incident glycosylat*" OR "getting glycosylat*" OR "prevalence of glycosylat*" OR "susceptib* to glycosylat*" OR "contribut* to glycosylat*" OR "development of glycosylat*" OR "develop* glycosylat*" OR "aggravat* glycosylat*" OR "resulted in glycosylat*") OR (endothelin-1-reduc* OR endothelin-1-inhibit* OR endothelin-1-decreas* OR endothelin-1-prevent* OR endothelin-1-suppress* OR endothelin-1-lessen* OR endothelin-1-lower* OR endothelin-1-mitigat* OR "endothelin-1 caus*" OR "caused by endothelin-1" OR "endothelin-1 induc*" OR "induced by endothelin-1" OR "endothelin-1 was due to" OR "endothelin-1 due to" OR "lead* to endothelin-1" OR "result* in endothelin-1" OR "role in endothelin-1" OR "endothelin-1 was produced by" OR "endothelin-1 produced by" OR "role in endothelin-1" OR "endothelin-1 provoked by" OR "endothelin-1 was provoked by" OR "provoked endothelin-1" OR "produce* endothelin-1" OR "endothelin-1 was produced by" OR "incidence of endothelin-1" OR "incident endothelin-1" OR "getting endothelin-1" OR "prevalence of endothelin-1" OR "susceptib* to endothelin-1" OR "contribut* to endothelin-1" OR "development of endothelin-1" OR "develop* endothelin-1" OR "aggravat* endothelin-1" OR "resulted in endothelin-1")

OR

(inflammation-reduc* OR inflammation-inhibit* OR inflammation-decreas* OR inflammation-prevent* OR inflammation-suppress* OR inflammation-lessen* OR inflammation-lower* OR inflammation-mitigat* OR "inflammation caus*" OR "caused by inflammation" OR "inflammation induc*" OR "induced by inflammation" OR "inflammation was due to" OR "inflammation due to" OR "lead* to inflammation" OR "result* in inflammation" OR "role in inflammation" OR "inflammation was produced by" OR "inflammation produced by" OR "role in inflammation" OR "inflammation provoked by" OR "inflammation was provoked by" OR "provoked inflammation" OR "produce* inflammation" OR "inflammation was produced by" OR "incidence of inflammation" OR "incident inflammation" OR "getting inflammation" OR "prevalence of inflammation" OR "susceptib* to inflammation" OR "contribut* to inflammation" OR "development of inflammation" OR "develop* inflammation" OR "aggravat* inflammation" OR "resulted in inflammation") OR (hypertension-reduc* OR hypertension-inhibit* OR hypertension-decreas* OR hypertension-prevent* OR hypertension-suppress* OR hypertension-lessen* OR hypertension-lower* OR hypertension-mitigat* OR "hypertension caus*" OR "caused by hypertension" OR "hypertension induc*" OR "induced by hypertension" OR "hypertension was due to" OR "hypertension due to" OR "lead* to hypertension" OR "result* in hypertension" OR "role in hypertension" OR "hypertension was produced by" OR "hypertension produced by" OR "role in hypertension" OR "hypertension provoked by" OR "hypertension was provoked by" OR "provoked hypertension" OR "produce* hypertension" OR "hypertension was produced by" OR "incidence of hypertension" OR "incident hypertension" OR "getting hypertension" OR "prevalence of hypertension" OR "susceptib* to hypertension" OR "contribut* to hypertension" OR "development of hypertension" OR "develop* hypertension" OR "aggravat* hypertension" OR "resulted in hypertension") OR ("insulin resistance reduc*" OR "insulin resistance inhibit*" OR "insulin resistance decreas*" OR "insulin resistance prevent*" OR "insulin resistance suppress*" OR "insulin resistance lessen*" OR "insulin resistance lower*" OR "insulin resistance mitigat*" OR "insulin resistance caus*" OR "caused by insulin resistance" OR "insulin resistance induc*" OR "induced by insulin resistance" OR "insulin resistance was due to" OR "insulin resistance due to" OR "lead* to insulin resistance" OR "result* in insulin resistance" OR "role in insulin resistance" OR "insulin resistance was produced by" OR "insulin resistance produced by" OR "role in insulin resistance" OR "insulin resistance provoked by" OR "insulin resistance was provoked by" OR "provoked insulin resistance" OR "produce* insulin resistance" OR "insulin resistance was produced by" OR "incidence of insulin resistance" OR "incident insulin resistance" OR "getting insulin resistance" OR "prevalence of insulin resistance" OR "susceptib* to insulin resistance" OR "contribut* to insulin resistance" OR "development of insulin resistance" OR "develop* insulin resistance" OR "aggravat* insulin resistance" OR "resulted in insulin resistance")

OR

(fibrosis-reduc* OR fibrosis-inhibit* OR fibrosis-decreas* OR fibrosis-prevent* OR fibrosis-suppress* OR fibrosis-lessen* OR fibrosis-lower* OR fibrosis-mitigat* OR "fibrosis caus*" OR "caused by fibrosis" OR "fibrosis induc*" OR "induced by fibrosis" OR "fibrosis was due to" OR "fibrosis due to" OR "lead* to fibrosis" OR "result* in fibrosis" OR "role in fibrosis" OR "fibrosis was produced by" OR "fibrosis produced by" OR "role in fibrosis" OR "fibrosis provoked by" OR "fibrosis was provoked by" OR "provoked fibrosis" OR "produce* fibrosis" OR "fibrosis was produced by" OR "incidence of fibrosis" OR "incident fibrosis" OR "getting fibrosis" OR "prevalence of fibrosis" OR "susceptib* to fibrosis" OR "contribut* to fibrosis" OR "development of fibrosis" OR "develop* fibrosis" OR "aggravat* fibrosis" OR

"resulted in fibrosis") OR ("metabolic syndrome reduc*" OR "metabolic syndrome inhibit*" OR "metabolic syndrome decreas*" OR "metabolic syndrome prevent*" OR "metabolic syndrome suppress*" OR "metabolic syndrome lessen*" OR "metabolic syndrome lower*" OR "metabolic syndrome mitigat*" OR "metabolic syndrome caus*" OR "caused by metabolic syndrome" OR "metabolic syndrome induc*" OR "induced by metabolic syndrome" OR "metabolic syndrome was due to" OR "metabolic syndrome due to" OR "lead* to metabolic syndrome" OR "result* in metabolic syndrome" OR "role in metabolic syndrome" OR "metabolic syndrome was produced by" OR "metabolic syndrome produced by" OR "role in metabolic syndrome" OR "metabolic syndrome provoked by" OR "metabolic syndrome was provoked by" OR "provoked metabolic syndrome" OR "produce* metabolic syndrome" OR "metabolic syndrome was produced by" OR "incidence of metabolic syndrome" OR "incident metabolic syndrome" OR "getting metabolic syndrome" OR "prevalence of metabolic syndrome" OR "susceptib* to metabolic syndrome" OR "contribut* to metabolic syndrome" OR "development of metabolic syndrome" OR "develop* metabolic syndrome" OR "aggravat* metabolic syndrome" OR "resulted in metabolic syndrome") OR (hyperglycemia-reduc* OR hyperglycemia-inhibit* OR hyperglycemia-decreas* OR hyperglycemia-prevent* OR hyperglycemia-suppress* OR hyperglycemia-lessen* OR hyperglycemia-lower* OR hyperglycemia-mitigat* OR "hyperglycemia caus*" OR "caused by hyperglycemia" OR "hyperglycemia induc*" OR "induced by hyperglycemia" OR "hyperglycemia was due to" OR "hyperglycemia due to" OR "lead* to hyperglycemia" OR "result* in hyperglycemia" OR "role in hyperglycemia" OR "hyperglycemia was produced by" OR "hyperglycemia produced by" OR "role in hyperglycemia" OR "hyperglycemia provoked by" OR "hyperglycemia was provoked by" OR "provoked hyperglycemia" OR "produce* hyperglycemia" OR "hyperglycemia was produced by" OR "incidence of hyperglycemia" OR "incident hyperglycemia" OR "getting hyperglycemia" OR "prevalence of hyperglycemia" OR "susceptib* to hyperglycemia" OR "contribut* to hyperglycemia" OR "development of hyperglycemia" OR "develop* hyperglycemia" OR "aggravat* hyperglycemia" OR "resulted in hyperglycemia")

OR

(nephropathy-reduc* OR nephropathy-inhibit* OR nephropathy-decreas* OR nephropathy-prevent* OR nephropathy-suppress* OR nephropathy-lessen* OR nephropathy-lower* OR nephropathy-mitigat* OR "nephropathy caus*" OR "caused by nephropathy" OR "nephropathy induc*" OR "induced by nephropathy" OR "nephropathy was due to" OR "nephropathy due to" OR "lead* to nephropathy" OR "result* in nephropathy" OR "role in nephropathy" OR "nephropathy was produced by" OR "nephropathy produced by" OR "role in nephropathy" OR "nephropathy provoked by" OR "nephropathy was provoked by" OR "provoked nephropathy" OR "produce* nephropathy" OR "nephropathy was produced by" OR "incidence of nephropathy" OR "incident nephropathy" OR "getting nephropathy" OR "prevalence of nephropathy" OR "susceptib* to nephropathy" OR "contribut* to nephropathy" OR "development of nephropathy" OR "develop* nephropathy" OR "aggravat* nephropathy" OR "resulted in nephropathy") OR (fibrogenesis-reduc* OR fibrogenesis-inhibit* OR fibrogenesis-decreas* OR fibrogenesis-prevent* OR fibrogenesis-suppress* OR fibrogenesis-lessen* OR fibrogenesis-lower* OR fibrogenesis-mitigat* OR "fibrogenesis caus*" OR "caused by fibrogenesis" OR "fibrogenesis induc*" OR "induced by fibrogenesis" OR "fibrogenesis was due to" OR "fibrogenesis due to" OR "lead* to fibrogenesis" OR "result* in fibrogenesis" OR "role in fibrogenesis" OR "fibrogenesis was produced by" OR "fibrogenesis produced by" OR "role in fibrogenesis" OR "fibrogenesis provoked by" OR "fibrogenesis

was provoked by" OR "provoked fibrogenesis" OR "produce* fibrogenesis" OR "fibrogenesis was produced by" OR "incidence of fibrogenesis" OR "incident fibrogenesis" OR "getting fibrogenesis" OR "prevalence of fibrogenesis" OR "susceptib* to fibrogenesis" OR "contribut* to fibrogenesis" OR "development of fibrogenesis" OR "develop* fibrogenesis" OR "aggravat* fibrogenesis" OR "resulted in fibrogenesis") OR ("arterial stiffness reduc*" OR "arterial stiffness inhibit*" OR "arterial stiffness decreas*" OR "arterial stiffness prevent*" OR "arterial stiffness suppress*" OR "arterial stiffness lessen*" OR "arterial stiffness lower*" OR "arterial stiffness mitigat*" OR "arterial stiffness caus*" OR "caused by arterial stiffness" OR "arterial stiffness induc*" OR "induced by arterial stiffness" OR "arterial stiffness was due to" OR "arterial stiffness due to" OR "lead* to arterial stiffness" OR "result* in arterial stiffness" OR "role in arterial stiffness" OR "arterial stiffness was produced by" OR "arterial stiffness produced by" OR "role in arterial stiffness" OR "arterial stiffness provoked by" OR "arterial stiffness was provoked by" OR "provoked arterial stiffness" OR "produce* arterial stiffness" OR "arterial stiffness was produced by" OR "incidence of arterial stiffness" OR "incident arterial stiffness" OR "getting arterial stiffness" OR "prevalence of arterial stiffness" OR "susceptib* to arterial stiffness" OR "contribut* to arterial stiffness" OR "development of arterial stiffness" OR "develop* arterial stiffness" OR "aggravat* arterial stiffness" OR "resulted in arterial stiffness") - title

OR (based on treatment MeSH terms)

2c. ("Adrenergic alpha-1 Receptor Antagonist*" OR "Adrenergic beta-Agonist*" OR "Adrenergic beta-Antagonist*" OR "Aldosterone Antagonist*" OR "Essential Amino Acid*" OR "Anabolic Agent*" OR "Androgen*" OR "Angiotensin II Type 1 Receptor Blockers*" OR "Angiotensin II Type 2 Receptor Blockers*" OR "Angiotensin Receptor Antagonist*" OR "Angiotensin-Converting Enzyme Inhibitor*" OR "Anti-Arrhythmia Agent*" OR "Monoclonal Antibodies" OR "Anticholesteremic Agent*" OR "Anticoagulant*" OR "Antifibrinolytic Agent*" OR "Antihypertensive*" OR "Anti-Inflammatory Agent*" OR "Antioxidant*" OR "Antithrombin*" OR "Antitubercular Agent*" OR "Anti-Ulcer Agent*" OR "Biological Availability" OR "Biosimilar Pharmaceutical*" OR "Blood Substitute*" OR "Bone Density Conservation Agent*" OR "Bone Morphogenetic Protein*" OR "Calcimimetic Agent*" OR "Calcium Channel Agonist*" OR "Calcium Channel Blocker*" OR "Caloric Restriction" OR "Cardiotonic Agent*" OR "Cardiovascular Agent*" OR "Chelating Agent*" OR "Colony-Stimulating Factor*" OR "Combined Modality Therapy" OR "Complement Inactivating Agent*" OR "Complement Inactivator Protein*" OR "Complementary Therap*" OR "Condiment*" OR "Cyclooxygenase Inhibitor*" OR "Cytoprotection" OR "Diabetic Diet*" OR "Diet Therap*" OR "Carbohydrate-Restricted diet*" OR "Fat-Restricted Diet*" OR "Mediterranean Diet*" OR "Protein-Restricted Diet*" OR "Sodium-Restricted Diet*" OR "Vegetarian Diet*" OR "Dietary Carbohydrates" OR "Dietary Fat*" OR "Dietary Fiber" OR "Dietary Protein*" OR "Dietary Supplement*" OR "Dietetics" OR "Dipeptidyl-Peptidase IV Inhibitor*" OR "Dose-Response Relationship*" OR "Drug Combination*" OR "Drug Discovery" OR "Drug Evaluation" OR "Drug Synergism" OR "Drug Therapy" OR "Drug Therapy" OR "Drug Utilization" OR "Investigational Drugs" OR "Embryonic Stem Cell*" OR "Energy Intake" OR "Enzyme Inhibitor*" OR "Estrogen*" OR "Exercise Therapy" OR "Fermentation" OR "Fetal Stem Cell*" OR "Fibrinolytic Agent*" OR "Flavonoid*" OR "Food Handling" OR "Formulated Food" OR "Free Radical Scavenger*" OR "Fruit*" OR "Gastrointestinal Agent*" OR "Gene Expression Regulation" OR "Gene Therapy" OR "Genetic Vector*" OR "Glycosaminoglycan*" OR "Health Food*" OR "Hematopoietic Stem Cell*" OR "Hirudin Therapy" OR "Horme*" OR "Human Growth Hormone*" OR "Hydroxymethylglutaryl-CoA Reductase Inhibitor*" OR

"Hypoglycemic Agent*" OR "Hypolipidemic Agent*" OR "Inflammation Mediator*" OR "Integrative Medicine" OR "Isoflavone*" OR "Leukotriene Antagonist*" OR "Chinese Traditional Medicine" OR "Traditional Medicine" OR "Mesenchymal Stem Cell*" OR "Micronutrient*" OR "Motor Activity" OR "Multipotent Stem Cell*" OR "Neuroprotective Agent*" OR "Nonprescription Drug*" OR "Nutrition Policy" OR "Nutrition Therapy" OR "Nutritional Physiological Phenomena" OR "Nutritional Requirement*" OR "Nutritional Science*" OR "Nutritional Support" OR "Parenteral Nutrition" OR "Peripheral Blood Stem Cell*" OR "Pharmaceutical Preparation*" OR "Pharmacokinetic*" OR "Phenol*" OR "Phosphodiesterase 5 Inhibitor*" OR "Phosphodiesterase Inhibitor*" OR "Phytoestrogen*" OR "Phytotherapy" OR "Plant Extract*" OR "Plant Leaves" OR "Plant Oil*" OR "Plant Preparation*" OR "Plant Protein*" OR "Plant Root*" OR "Medicinal Plant*" OR "Platelet Aggregation Inhibitor*" OR "Pluripotent Stem Cell*" OR "Polyphenol*" OR "Prebiotic*" OR "Prescription Drug*" OR "Primary Prevention" OR "Probiotic*" OR "Protease Inhibitor*" OR "Protective Agent*" OR "Protein Kinase Inhibitor*" OR "Recombinant Protein*" OR "Regeneration" OR "Seed*" OR "Selective Estrogen Receptor Modulator*" OR "Sodium Chloride Symporter Inhibitor*" OR "Sodium Potassium Chloride Symporter Inhibitor*" OR "Stem Cell Transplantation" OR "Stem Cell*" OR "Steroid*" OR "Stromal Cell*" OR "Synbiotic*" OR "Thrombolytic Therapy" OR "Tissue Therapy" OR "Treatment Outcome" OR "Vasodilator Agent*" OR "Vegetable Protein*" OR "Vegetable*") near/5 (glycat* OR "peripheral vascular disease" OR arteriosclerosis OR vasoconstriction OR glycosylat* OR endothelin-1 OR inflammation OR hypertension OR "insulin resistance" OR fibrosis OR "metabolic syndrome" OR hyperglycemia OR nephropathy OR fibrogenesis OR "arterial stiffness") - title

3. **MESH QUALIFIERS - MESH HEADING**

3a. ("kidney failure, chronic/diet therapy" OR "renal insufficiency, chronic/diet therapy" OR "Diabetic Nephropathies/diet therapy" OR Nephrosclerosis/diet therapy OR Nephrosis/diet therapy OR Nephritis/diet therapy OR "Nephritis, Interstitial/diet therapy") OR ("kidney failure, chronic/drug therapy" OR "renal insufficiency, chronic/drug therapy" OR "Diabetic Nephropathies/drug therapy" OR Nephrosclerosis/drug therapy OR Nephrosis/drug therapy OR Nephritis/drug therapy OR "Nephritis, Interstitial/drug therapy") OR ("kidney failure, chronic/prevention & control" OR "renal insufficiency, chronic/prevention & control" OR "Diabetic Nephropathies/prevention & control" OR Nephrosclerosis/prevention & control OR Nephrosis/prevention & control OR Nephritis/prevention & control OR "Nephritis, Interstitial/prevention & control") OR ("kidney failure, chronic/pharmacology" OR "renal insufficiency, chronic/pharmacology" OR "Diabetic Nephropathies/pharmacology" OR Nephrosclerosis/pharmacology OR Nephrosis/pharmacology OR Nephritis/pharmacology OR "Nephritis, Interstitial/pharmacology")

4. **MESH GENERIC TERMS - MESH HEADING NO EXPLODE**

(Extracted from 441 Treatment MeSH terms of CKD core analysis, with some related additions)

4a. (Adrenergic alpha-1 Receptor Antagonists OR Adrenergic beta-Agonists OR Adrenergic beta-Antagonists OR Aldosterone Antagonists OR Amino Acids OR Amino Acids, Essential OR Anabolic Agents OR Androgens OR Angiotensin II Type 1 Receptor Blockers OR Angiotensin II Type 2 Receptor Blockers OR Angiotensin Receptor Antagonists OR Angiotensin-Converting Enzyme Inhibitors OR Anti-Arrhythmia Agents OR Antibodies, Monoclonal OR Anticholesteremic Agents OR Anticoagulants OR Antifibrinolytic Agents OR Antihypertensive Agents OR Anti-Inflammatory Agents OR Anti-Inflammatory Agents, Non-

Steroidal OR Antioxidants OR Antithrombins OR Antitubercular Agents OR Anti-Ulcer Agents OR Biological Availability OR Biosimilar Pharmaceuticals OR Blood Substitutes OR Bone Density Conservation Agents OR Bone Morphogenetic Proteins OR Calcimimetic Agents OR Calcium Channel Agonists OR Calcium Channel Blockers OR Caloric Restriction OR Cardiotonic Agents OR Cardiovascular Agents OR Chelating Agents OR Colony-Stimulating Factors OR Combined Modality Therapy OR Complement Inactivating Agents OR Complement Inactivator Proteins OR Complementary Therapies OR Condiments OR Cyclooxygenase Inhibitors OR Cytoprotection OR Diabetic Diet OR Diet OR Diet Therapy OR Diet, Carbohydrate-Restricted OR Diet, Fat-Restricted OR Diet, Mediterranean OR Diet, Protein-Restricted OR Diet, Sodium-Restricted OR Diet, Vegetarian OR Dietary Carbohydrates OR Dietary Fats OR Dietary Fats, Unsaturated OR Dietary Fiber OR Dietary Proteins OR Dietary Supplements OR Dietetics OR Dipeptidyl-Peptidase IV Inhibitors OR Dose-Response Relationship, Drug OR Drug Combinations OR Drug Discovery OR Drug Evaluation, Preclinical OR Drug Synergism OR Drug Therapy OR Drug Therapy, Combination OR Drug Utilization OR Drugs, Investigational OR Embryonic Stem Cells OR Energy Intake OR Enzyme Inhibitors OR Estrogens OR Estrogens, Conjugated (USP) OR Estrogens, Non-Steroidal OR Exercise OR Exercise Therapy OR Fermentation OR Fetal Stem Cells OR Fibrinolytic Agents OR Flavonoids OR Food OR Food Handling OR Food, Formulated OR Free Radical Scavengers OR Fruit OR Gastrointestinal Agents OR Gene Expression Regulation OR Gene Therapy OR Genetic Vectors OR Glycosaminoglycans OR Health Food OR Hematopoietic Stem Cell Transplantation OR Hematopoietic Stem Cells OR Hirudin Therapy OR Hirudins OR Hormesis OR Human Growth Hormone OR Hydroxymethylglutaryl-CoA Reductase Inhibitors OR Hypoglycemic Agents OR Hypolipidemic Agents OR Inflammation Mediators OR Integrative Medicine OR Isoflavones OR Leukotriene Antagonists OR Medicine, Chinese Traditional OR Medicine, Traditional OR Mesenchymal Stem Cell Transplantation OR Micronutrients OR Motor Activity OR Multipotent Stem Cells OR Neuroprotective Agents OR Nonprescription Drugs OR Nutrition Policy OR Nutrition Therapy OR Nutritional Physiological Phenomena OR Nutritional Requirements OR Nutritional Sciences OR Nutritional Support OR Parenteral Nutrition OR Peripheral Blood Stem Cell Transplantation OR Pharmaceutical Preparations OR Pharmacokinetics OR Phenols OR Phosphodiesterase 5 Inhibitors OR Phosphodiesterase Inhibitors OR Phytoestrogens OR Phytotherapy OR Plant Extracts OR Plant Leaves OR Plant Oils OR Plant Preparations OR Plant Proteins OR Plant Roots OR Plants, Medicinal OR Platelet Aggregation Inhibitors OR Pluripotent Stem Cells OR Polyphenols OR Prebiotics OR Prescription Drugs OR Primary Prevention OR Probiotics OR Protease Inhibitors OR Protective Agents OR Protein Kinase Inhibitors OR Recombinant Proteins OR Regeneration OR Seeds OR Selective Estrogen Receptor Modulators OR Sodium Chloride Symporter Inhibitors OR Sodium Potassium Chloride Symporter Inhibitors OR Stem Cell Transplantation OR Stem Cells OR Steroids OR Stromal Cells OR Synbiotics OR Thrombolytic Therapy OR Tissue Therapy OR Treatment Outcome OR Vasodilator Agents OR Vegetable Proteins OR Vegetables) - MeSH Hdg No Expl

(The following is a reduced version of MeSH terms [terms highlighted above] that was necessary to avoid the timeout problem)

4b. (Antioxidants OR Caloric Restriction OR Complementary Therapies OR Condiments OR Diet Therapy OR Dietary Fiber OR Dietary Supplements OR Embryonic Stem Cells OR Energy Intake OR Exercise OR Exercise Therapy OR Fermentation OR Fetal Stem Cells OR Fibrinolytic Agents OR Flavonoids OR Health Food OR Hematopoietic Stem Cell Transplantation OR Hematopoietic Stem Cells OR Hormesis OR Inflammation Mediators OR Integrative Medicine OR Isoflavones OR Mesenchymal Stem Cell

Transplantation OR Multipotent Stem Cells OR Nutrition Therapy OR Peripheral Blood Stem Cell Transplantation OR Phenols OR Phytoestrogens OR Phytotherapy OR Plant Extracts OR Plant Leaves OR Plant Oils OR Plant Preparations OR Plant Proteins OR Plant Roots OR Plants, Medicinal OR Pluripotent Stem Cells OR Polyphenols OR Prebiotics OR Primary Prevention OR Probiotics OR Protective Agents OR Regeneration OR Seeds OR Stem Cell Transplantation OR Stem Cells OR Stromal Cells OR Synbiotics OR Vegetable Proteins OR Vegetables)

4c. (treat* OR therap* OR cure* OR intervention* OR rehabilitat* OR monotherap* OR pretreat* OR psychotherap* OR pharmacotherap* OR medication* OR drug* OR stimulant* OR pharmacological* OR diet* OR supplementation OR renoprotect* OR nephroprotect* OR "prevent* progressi*" OR "retard* the progressi*" OR "delay* the progressi*" OR "reduc* the progressi*" OR "attenuat* the progressi*" OR "halt* the progressi*" OR "inhibit* the progressi*" OR "suppress* the progressi*" OR "alleviat* the progressi" OR "oppos* the progressi" OR "imped* the progressi*" OR "limit* the progressi*" OR "ameliorat* the progressi*" OR protect* OR alleviate* OR ameliorate* OR improv* OR benefit*)

AND

USE NEGATION TERMS FROM #2

NOT (hypertension-reduc* OR hypertension-inhibit* OR hypertension-decreas* OR hypertension-prevent* OR hypertension-suppress* OR hypertension-lessen* OR hypertension-lower* OR hypertension-mitigat* OR "hypertension caus*" OR "caused by hypertension" OR "hypertension induc*" OR "induced by hypertension" OR "hypertension was due to" OR "hypertension due to" OR "lead* to hypertension" OR "result* in hypertension" OR "role in hypertension" OR "hypertension was produced by" OR "hypertension produced by" OR "role in hypertension" OR "hypertension provoked by" OR "hypertension was provoked by" OR "provoked hypertension" OR "produce* hypertension" OR "hypertension was produced by" OR "incidence of hypertension" OR "incident hypertension" OR "getting hypertension" OR "prevalence of hypertension" OR "susceptib* to hypertension" OR "contribut* to hypertension" OR "development of hypertension" OR "develop* hypertension" OR "aggravat* hypertension" OR "resulted in hypertension")) - title

1C2. Non-CKD Literature Treatments

(to reduce retrieval volume, fifteen symptoms were selected, and all combinations of two symptoms were generated for title): (glycat* OR "peripheral vascular disease" OR arteriosclerosis OR vasoconstriction OR glycosylat* OR endothelin-1 OR inflammation OR hypertension OR "insulin resistance" OR fibrosis OR "metabolic syndrome" OR hyperglycemia OR nephropathy OR fibrogenesis OR "arterial stiffness")

Query=#(1a NOT (#1b OR #1c OR #1d OR 2b)) AND ((2a OR 2c OR (3a AND 3b) OR (4a AND 4b))

1a. **TITLE PLUS MESH (use title only for demonstration)**

(glycat* AND "peripheral vascular disease") OR (glycat* AND arteriosclerosis) OR (glycat* AND vasoconstriction) OR (glycat* AND glycosylat*) OR (glycat* AND endothelin-1) OR (glycat* AND Inflammation) OR (glycat* AND hypertension) OR (glycat* AND "insulin resistance") OR (glycat* AND fibrosis) OR (glycat* AND "metabolic syndrome") OR (glycat* AND hyperglycemia) OR (glycat* AND Nephropathy) OR (glycat* AND fibrogenesis) OR (glycat* AND "arterial stiffness") OR ("peripheral vascular disease" AND arteriosclerosis) OR ("peripheral vascular disease" AND vasoconstriction) OR ("peripheral vascular disease" AND glycosylat*) OR ("peripheral vascular disease" AND endothelin-1) OR ("peripheral vascular disease" AND Inflammation) OR ("peripheral vascular disease" AND hypertension) OR ("peripheral vascular disease" AND "insulin resistance") OR ("peripheral vascular disease" AND fibrosis) OR ("peripheral vascular disease" AND "metabolic syndrome") OR ("peripheral vascular disease" AND hyperglycemia) OR ("peripheral vascular disease" AND Nephropathy) OR ("peripheral vascular disease" AND fibrogenesis) OR ("peripheral vascular disease" AND "arterial stiffness") OR (arteriosclerosis AND vasoconstriction) OR (arteriosclerosis AND glycosylat*) OR (arteriosclerosis AND endothelin-1) OR (arteriosclerosis AND Inflammation) OR (arteriosclerosis AND hypertension) OR (arteriosclerosis AND "insulin resistance") OR (arteriosclerosis AND fibrosis) OR (arteriosclerosis AND "metabolic syndrome") OR (arteriosclerosis AND hyperglycemia) OR (arteriosclerosis AND Nephropathy) OR (arteriosclerosis AND fibrogenesis) OR (arteriosclerosis AND "arterial stiffness") OR (vasoconstriction AND glycosylat*) OR (vasoconstriction AND endothelin-1) OR (vasoconstriction AND Inflammation) OR (vasoconstriction AND hypertension) OR (vasoconstriction AND "insulin resistance") OR (vasoconstriction AND fibrosis) OR (vasoconstriction AND "metabolic syndrome") OR (vasoconstriction AND hyperglycemia) OR (vasoconstriction AND Nephropathy) OR (vasoconstriction AND fibrogenesis) OR (vasoconstriction AND "arterial stiffness") OR (glycosylat* AND endothelin-1) OR (glycosylat* AND Inflammation) OR (glycosylat* AND hypertension) OR (glycosylat* AND "insulin resistance") OR (glycosylat* AND fibrosis) OR (glycosylat* AND "metabolic syndrome") OR (glycosylat* AND hyperglycemia) OR (glycosylat* AND Nephropathy) OR (glycosylat* AND fibrogenesis) OR (glycosylat* AND "arterial stiffness") OR (endothelin-1 AND Inflammation) OR (endothelin-1 AND hypertension) OR (endothelin-1 AND "insulin resistance") OR (endothelin-1 AND fibrosis) OR (endothelin-1 AND "metabolic syndrome") OR (endothelin-1 AND hyperglycemia) OR (endothelin-1 AND Nephropathy) OR (endothelin-1 AND fibrogenesis) OR (endothelin-1 AND "arterial stiffness") OR (Inflammation AND hypertension) OR (Inflammation AND "insulin resistance") OR (Inflammation AND fibrosis) OR (Inflammation AND "metabolic syndrome") OR (Inflammation AND hyperglycemia) OR (Inflammation AND Nephropathy) OR (Inflammation AND fibrogenesis) OR (Inflammation AND "arterial stiffness") OR (hypertension AND "insulin resistance") OR (hypertension AND fibrosis) OR (hypertension AND

"metabolic syndrome") OR (hypertension AND hyperglycemia) OR (hypertension AND Nephropathy) OR (hypertension AND fibrogenesis) OR (hypertension AND "arterial stiffness") OR ("insulin resistance" AND fibrosis) OR ("insulin resistance" AND "metabolic syndrome") OR ("insulin resistance" AND hyperglycemia) OR ("insulin resistance" AND Nephropathy) OR ("insulin resistance" AND fibrogenesis) OR ("insulin resistance" AND "arterial stiffness") OR (fibrosis AND "metabolic syndrome") OR (fibrosis AND hyperglycemia) OR (fibrosis AND Nephropathy) OR (fibrosis AND fibrogenesis) OR (fibrosis AND "arterial stiffness") OR ("metabolic syndrome" AND hyperglycemia) OR ("metabolic syndrome" AND Nephropathy) OR ("metabolic syndrome" AND fibrogenesis) OR ("metabolic syndrome" AND "arterial stiffness") OR (hyperglycemia AND Nephropathy) OR (hyperglycemia AND fibrogenesis) OR (hyperglycemia AND "arterial stiffness") OR (Nephropathy AND fibrogenesis) OR (Nephropathy AND "arterial stiffness") OR (fibrogenesis AND "arterial stiffness")

NOT

1b. ("kidney failure, chronic" OR "renal insufficiency, chronic" OR "Diabetic Nephropathies" OR Nephrosclerosis OR Nephrosis OR Nephritis OR "Nephritis, Interstitial") - MeSH Heading

OR

1c. "chronic kidney disease" OR "cystic fibrosis" - topic

OR

(treatments from CKD core literature analysis)

1d. "15(R/S)-methyl- lipoxin A(4)" OR "15-deoxyspergualin" OR "2-(8-hydroxy-6-methoxy-1-oxo-1h-2-benzopyran-3-yl) propionic acid" OR "22-oxacalcitriol" OR "3-hydroxy-3-methylglutaryl" OR "3-hydroxy-DL-kynurenine" OR "3-methoxy-4-propargyloxycinnamoyl anthranilate" OR "4-phenylbutyric acid" OR "5-aminosalicylic acid" OR "5-HT(2A) receptor C-terminus" OR "5-methyltetrahydrofolate" OR "7-O-galloyl-D-sedoheptulose" OR "Abatacept" OR "abciximab" OR "Abelmoschus manihot" OR "Abetimus sodium" OR "ABT-627" OR "Acacia gum" OR "Acacia nilotica pods extract" OR "acarbose" OR "acetaminophen" OR "acetazolamide" OR "acetylcysteine" OR "Acetylsalicylic Acid" OR "ACTH" OR "acupuncture" OR "adalimumab" OR "Adaptive servo-ventilation" OR "Adenosine 3', 5' cyclic monophosphate" OR "adrenocorticotropic hormone*" OR "adrenocorticotropin" OR "adrenomedullin" OR "adriamycin" OR "aerobic exercise" OR "AG490" OR "agalsidase alfa" OR "Agmatine" OR "alagebrium" OR "albendazole" OR "albumin" OR "alendronate" OR "alfacalcidol" OR "aliskiren" OR "Allopurinol" OR "All-trans-retinoic acid" OR "alpha3(IV)NC1" OR "alphacalcidiol" OR "alpha-galactosidase" OR "alpha-galactosylceramide" OR "alpha-lipoic-acid" OR "alpha-spinasterol" OR "alpha-tocopherol" OR "alprostadil" OR "ALT-946" OR "aluminum" OR "ambrisentan" OR "amikacin" OR "amiloride" OR "aminoguanidine" OR "aminopenicillins" OR "amitriptyline" OR "amlodipine" OR "amoxicillin" OR "amphotericin" OR "ampicillin" OR "ampicillin-sulbactam" OR "Anakinra" OR "anastrozole" OR "androgen*" OR "Andrographolide" OR "Angiostatin*" OR "angiotensin-(1-7)" OR "Anthranilic acid" OR "antisense oligodeoxynucleotide near/3 CK2alpha" OR "Antroquinonol" OR "Apelin" OR "apheresis near/1 therapy" OR "Apocynin" OR "aprotinin" OR "Arabic gum" OR "aranesp" OR "arginine" OR "artemisinin" OR "artery bypass" OR "artery revascularization" OR "artery stent*" OR "Artesunate" OR "Artocarpus communis" OR "artonin E" OR "AS101" OR "ascorbic acid" OR "a-series

gangliosides" OR "Aspirin" OR "AST-120" OR "astaxanthin" OR "astilbin" OR "Astragali" OR "Astragaloside IV" OR "Astragalus" OR "asymmetric dimethylarginine" OR "atenolol" OR "Atorvastatin" OR "atra" OR "atrasentan" OR "AVE7688" OR "Avosentan" OR "Azathioprine" OR "azelnidipine" OR "azuki bean*" OR "B12" OR "Bacillus Calmette-Guerin vaccine" OR "balloon angioplasty" OR "balneotherapy" OR "baoyuan dahuang" OR "bardoxolone methyl" OR "bare metal stent*" OR "bariatric surgery" OR "batroxobin" OR "belatacept" OR "belimumab" OR "benazepril" OR "benfotiamine" OR "benidipine" OR "benzbromarone" OR "benzodiazepine" OR "Beraprost sodium" OR "Berberine" OR "beta-carotene" OR "beta-D-mannuronic acid" OR "Beta-galactosylceramide" OR "betaine" OR "beta-Lactams" OR "Bezafibrate" OR "BG9588" OR "bicarbonate" OR "Bifidobacterium" OR "bilirubin" OR "biliverdin" OR "bindarit" OR "bisoprolol" OR "bisphosphonate" OR "bitter gourd" OR "Bivalirudin" OR "blood stem cell transplantation" OR "blood transfusions" OR "BMP-7" OR "BMS" OR "bone marrow transplantation" OR "Bone morphogenic protein-7" OR "bortezomib" OR "bosentan" OR "Boswellia" OR "BQ-123" OR "bright-light phototherapy" OR "B-type natriuretic peptide" OR "Bupleurum falcatum" OR "Bupleurum polysaccharides" OR "Bupleurum scorzoneraefolium" OR "Bushen Huoxue" OR "Bushen Jianpi Huoxue Paidu" OR "Butein" OR "Caffeic acid phenethyl ester" OR "calcidiol" OR "calcitonin" OR "calcitriol" OR "calcium acetate" OR "calcium carbonate" OR "calcium dobesilate" OR "calcium hydroxyapatite" OR "calcium supplement*" OR "Calori* restrict*" OR "camostat mesilate" OR "candesartan" OR "cannabinoid*" OR "Capoten" OR "capsaicin" OR "captopril" OR "carbapenems" OR "carnitine" OR "Carnosine" OR "carvedilol" OR "casein" OR "catechin*" OR "CD37" OR "cefadroxil" OR "cefazolin" OR "cefepime" OR "cefixime" OR "cefotaxime" OR "cefotiam" OR "ceftazidime" OR "ceftibuten" OR "ceftriaxone" OR "Cefuroxime" OR "CEP-33779" OR "cephalexin" OR "cephalosporin" OR "cephoxitin" OR "cerivastatin" OR "Chailing" OR "charcoal" OR "chelat* therapy" OR "Chembridge-5861528" OR "chenodeoxycholic acid" OR "cherries" OR "chitosan" OR "chitosan-coated dialdehyde cellulose" OR "chlorambucil" OR "Chlorella pyrenoidosa" OR "chloroquine" OR "Chlorthalidone" OR "cholecalciferol" OR "Chromium" OR "chronotherapy" OR "ciclosporin" OR "Ciglitazone" OR "cilazapril" OR "cilnidipine" OR "Cilostazol" OR "cinacalcet" OR "cinnamic aldehyde" OR "cinnamon oil" OR "cinnamoyl anthranilates" OR "ciprofloxacin" OR "cladribine" OR "Clarithromycin" OR "clarithromycin" OR "clavulanic acid" OR "clodronate" OR "clofibrate" OR "clofibric acid" OR "Clonazepam" OR "clonidine" OR "clopidogrel" OR "Cnidium officinale Makino" OR "cobalt" OR "Coenzyme Q10" OR "colchicine" OR "colforsin daropate hydrochloride" OR "Colistin" OR "colquhounia root" OR "Cordyceps sinensis" OR "Corni Fructus" OR "Cornus officinalis" OR "coronary revascularization" OR "cotrimoxazole" OR "co-trimoxazole" OR "CR2-Crry" OR "CR2-fH" OR "cranberry extract near/3 Zuravit" OR "C-reactive protein" OR "Cryoapheresis" OR "Cryptococcus neoformans" OR "CS-866" OR "CTLA4 immunoglobulin" OR "curantil" OR "curcumin" OR "CYC202" OR "cycloferon" OR "Cyclophosphamide" OR "cyclosporin" OR "cyclosporine" OR "cyprophloxacin" OR "cysteamine" OR "Cytapheresis" OR "Daflon" OR "dalfopristin" OR "D-alpha-tocopherol" OR "damp-heat" OR "Dan Shao Tang" OR "Danggui buxue tang" OR "Daptomycin" OR "darbepoetin" OR "darusentan" OR "decorin gene transfection" OR "Defibrase" OR "Deflazacort" OR "Deflux" OR "dehydroepiandrosterone " OR "delapril" OR "denosumab" OR "Dermatan sulfate" OR "DES implantation" OR "desmopressin" OR "dexamethasone" OR "dextranomer" OR "DHEA" OR "dialysis" OR "diclofenac" OR "dietary fiber" OR "diet* near/3 n-3 lipids" OR "diet* near/3 n-6 lipids" OR "diet* near/3 phosphate restrict*" OR "diet* near/3 protein restrict*" OR "dietary soy" OR "digoxin" OR "Dihuang" OR "dihydropyridine" OR "dihydrotestosterone" OR "dilazep" OR "diltiazem" OR "diphenylene iodinium" OR "dipyridamole" OR "diuretic" OR "DNA vaccination" OR "dobutamine" OR

"docosahexaenoic acid" OR "Dolabi " OR "dopamine" OR "doripenem" OR "doxazosin" OR "doxepin" OR "doxercalciferol" OR "doxorubicin" OR "Doxycycline" OR "D-penicillamine" OR "drug-eluting stent*" OR "duloxetine" OR "E4177" OR "ebselen" OR "eculizumab" OR "edaravone" OR "Efonidipine" OR "eicosapentaenoic acid" OR "electroporation" OR "emodin" OR "enalapril" OR "endoglycosidase S" OR "EndoS" OR "enoxaparin" OR "entecavir" OR "epigallocatechin-3-gallate" OR "epinephrine" OR "eplerenone" OR "EPO" OR "epoetin" OR "Epoxyeicosatrienoic acid*" OR "Epratuzumab" OR "Eprex" OR "Eprodisate" OR "eprosartan" OR "epsilon-aminocaproic acid" OR "ergocalciferol" OR "ergone" OR "Eritrichium sericeum" OR "ertapenem" OR "erythromycin" OR "erythropoietin" OR "ESA" OR "essential amino acid*" OR "estradiol" OR "estrogen" OR "ESWL" OR "etanercept" OR "ethanol" OR "ethanolic" OR "ethyl-icosapentate" OR "etidronate" OR "etodolac" OR "Euonymus alatus" OR "everolimus" OR "exendin-4" OR "extracorporeal shock-wave lithotripsy" OR "ezetimibe" OR "falecalcitriol" OR "fasudil" OR "Fc fusion protein" OR "Febuxostat" OR "felodipine" OR "fengbei huayu" OR "Fenofibrate" OR "fenoldopam" OR "ferric carboxymaltose" OR "ferric gluconate" OR "ferulic acid" OR "Ferumoxytol" OR "fetuin-A" OR "FG-3019" OR "fish oil" OR "FK506" OR "flaxseed" OR "fluconazole" OR "fludarabine" OR "fluoroquinolone*" OR "fluvastatin" OR "folate" OR "folic acid" OR "fondaparinux" OR "fosfomycin" OR "fosinopril" OR "FR167653" OR "frusemide" OR "fucoidan" OR "Fufang Xueshuantong Capsule" OR "furosemide" OR "Fuzheng Huayu recipe" OR "G. inflata" OR "gabapentin" OR "gabexate mesylate" OR "Gamma linolenic acid" OR "gammaglobulin" OR "gangleron-electrophoresis with sinusoidal modulated currents" OR "Ganoderma lucidum" OR "garlic" OR "gatifloxacin" OR "GBCA" OR "gentamicin" OR "Ghrelin" OR "Ginger" OR "Ginkgo biloba" OR "Ginseng" OR "ginsenoside Rg1" OR "glabridin" OR "glibenclamide" OR "gliclazide" OR "glimepiride" OR "gliotoxin" OR "Glitazones" OR "glutamine" OR "gluten-free diet*" OR "Glycyrrhiza uralensis" OR "grape seed extract" OR "Green tea" OR "Growth Hormone*" OR "guava fruit" OR "GW501516" OR "GW9662" OR "gymnemic acid" OR "Hachimi-jio-gan" OR "Hatha yoga" OR "heat-producing needling" OR "Hematide" OR "hemin" OR "heparan sulfate" OR "heparin" OR "hepatocyte growth factor" OR "hepcidin" OR "Hibiscus sabdariffa Linnaeus" OR "hirudin*" OR "HOE 140" OR "Honokiol" OR "Hormonal adjuvants" OR "hormone replacement therapy" OR "Huang" OR "Huangqi" OR "Huayu" OR "human erythropoietin" OR "human growth hormone*" OR "Huoxue" OR "hyaluronic acid" OR "hyaluronic acid copolymer" OR "hydralazine" OR "hydration" OR "hydrochlorothiazide" OR "hydrocortisone" OR "Hydroxiapatite" OR "Hydroxychloroquine" OR "hydroxyurea" OR "Hyperbaric oxygen" OR "hypoproteic diet*" OR "hypotonic intravenous fluid" OR "Ichnocarpus frutescens" OR "IDEC-131" OR "IdeS" OR "IGF-1" OR "IgG glycan hydrolysis" OR "IgG-degrading enzyme of S.pyogenes" OR "IL-10" OR "IL-11" OR "IL-1Ra" OR "Iloprost" OR "imatinib" OR "imidapril" OR "Imipenem" OR "immunoglobulin G" OR "incretin" OR "indapamide" OR "indinavir" OR "Indole-3-carbinol" OR "indomethacin" OR "infliximab" OR "Insulin" OR "insulin-like growth factor*" OR "intelligent near/3 nanoparticle*" OR "interference therapy" OR "interferon*" OR "interleukin-10" OR "Interleukin-11" OR "Interleukin-4" OR "iododoxorubicin" OR "Irbesartan" OR "irinotecan" OR "iron dextran" OR "iron sucrose" OR "iron supplementation" OR "iron therapy" OR "Irradiation" OR "islet cell transplantation" OR "isoflavone" OR "Isotretinoin" OR "isradipine" OR "itraconazole" OR "Jianpi Qinghua" OR "ju-ling-tang" OR "keto acids" OR "ketoacids" OR "keto-analogues" OR "ketoconazole" OR "KF24345" OR "kidney transplant*" OR "Kremezin" OR "labetalol" OR "lacidipine" OR "Lactobacillus reuteri GMNL-263" OR "LAF237" OR "Laminaria japonica" OR "lamivudine" OR "lansoprazole" OR "lanthanum carbonate" OR "l-arginine" OR "laser radiation" OR "laser therapy" OR "lasix" OR "lazaroid" OR "leflunomide" OR "Lei Gong Teng Radix et Rhizoma Tripterygii" OR "lenalidomide" OR "lercanidipine"

OR "Lespedeza michx" OR "leukocytapheresis" OR "leupeptin" OR "levamisole" OR "levofloxacin" OR "licochalcone A" OR "licorisoflavan A" OR "Ligustrazine" OR "linagliptin" OR "linezolid" OR "linoleic acid" OR "LIPIN" OR "lipoic acid" OR "lisinopril" OR "lithotripsy" OR "Liuwei Dihuang" OR "LJP 394" OR "loganin" OR "losartan" OR "lovastatin" OR "low-casein diet*" OR "Low-dose radiation" OR "low-fat dairy products" OR "low-phosphorous" OR "low-protein diet*" OR "low-salt diet*" OR "low-sodium" OR "LR-74" OR "LR-9" OR "LR-90" OR "LSKL" OR "LU 135252" OR "lumbrukinase" OR "LY333531" OR "Lysozyme" OR "M2000" OR "Magnesium" OR "magnetolaserotherapy" OR "Magnolia biondii" OR "Magnolia officinalis" OR "magnolol" OR "mai-luo-tong" OR "manidipine" OR "mannitol" OR "man-shen-ling" OR "maxacalcitol" OR "mecillinam" OR "Mediterranean diet" OR "medoxomil" OR "Megestrol acetate" OR "melanocortin" OR "melatonin" OR "meloxicam" OR "melphalan" OR "meprinbeta" OR "mesenchymal stem cells" OR "Mesenchymal stromal cells" OR "metanephric mesenchymal cells" OR "Metformin" OR "methionine" OR "methotrexate" OR "methoxy polyethylene glycol-epoetin beta" OR "methyl prednisolone" OR "Methyldopa" OR "methylene blue" OR "methylprednisolone" OR "Metoprolol" OR "metronidazole" OR "MG132" OR "microwave resonance therapy" OR "microwaves" OR "miglitol" OR "Milk thistle extract" OR "miltiorrhiza" OR "mineral water" OR "mirtazapine" OR "misoprostol" OR "mitochondria-targeted ubiquinone" OR "MitoQ " OR "mizoribine" OR "MMF" OR "mNOX-E36" OR "molecular adsorbent recirculating system" OR "molsidomine" OR "Monascus purpureus Went rice" OR "monoclonal antibodies to B-cell markers" OR "monoclonal antibody (mAb) for ICOS" OR "Monoclonal immunoglobulin G1" OR "monopril" OR "montelukast" OR "morphine sulphate" OR "Morroniside" OR "Morus alba" OR "morusin" OR "moxonidine" OR "mycophenolate mofetil" OR "mycophenolate sodium" OR "mycophenolic acid" OR "myo-inositol" OR "myricetin" OR "MZR treatment" OR "N-acetylcysteine" OR "N-acetyl-seryl-aspartyl-lysyl-proline" OR "Nandrolone decanoate" OR "nanocarrier complex*" OR "Nateglinide" OR "natural Indigo" OR "NCTD" OR "Nebivolol" OR "nelfinavir" OR "nephrolithiasis" OR "nephrolitholapaxy" OR "nephrolithotomy" OR "NESP" OR "netilmicin" OR "Neu5Ac" OR "neuraminidase" OR "Niacin" OR "Niaoduqing" OR "niceritrol" OR "nicorandil" OR "nifedipine" OR "nilvadipine" OR "Nitrendipine" OR "nitrofurantoin" OR "nitroglycerin" OR "nitro-oleic acid" OR "Norcantharidin" OR "norepinephrine" OR "norfloxacin" OR "Notoginseng" OR "novel erythropoiesis stimulating protein" OR "NOX-A12" OR "NPS R-568" OR "Octreotide" OR "ofloxacin" OR "oleanolic acid" OR "Olmesartan" OR "omapatrilat" OR "omega-3" OR "omeprazole" OR "ondansetron" OR "ONO-1301" OR "ophloxacin" OR "Opioids" OR "orlistat" OR "oseltamivir" OR "osteoprotegerin" OR "Oxalobacter formigenes" OR "oxycodone" OR "p21" OR "paclitaxel" OR "paeony" OR "paidu baoshen" OR "palm-oil near/3 Tocotrienol-rich-fraction" OR "pamidronate" OR "Panax ginseng" OR "Panax notoginseng" OR "pancreas transplantation" OR "paracetamol" OR "paricalcitol" OR "paroxetine" OR "parthenolide" OR "PD123319" OR "PDL-1" OR "pectin" OR "PEDF" OR "pefloxacin" OR "Peginesatide" OR "penicillin" OR "pentosan polysulfate" OR "pentoxifylline" OR "pephloxacin" OR "Perilla frutescens" OR "perindopril" OR "persantine" OR "Phellodendri Cortex" OR "phenacetin" OR "Phlorizin" OR "phosphorus restriction" OR "photopheresis" OR "phycocyanin" OR "phycocyanobilin" OR "Phytoestrogens" OR "Phytolacca americana" OR "picrorhiza" OR "pimagedine" OR "pioglitazone" OR "piperacillin" OR "pirfenidone" OR "Pitavastatin" OR "pivmecillinam" OR "plasma exchange therapy" OR "plasmapheresis" OR "plastoquinone" OR "policosanol" OR "polydimethylsiloxane" OR "polyethylene glycol" OR "Polygonum capitatum" OR "polymyxin B" OR "polyoxidonium" OR "polyunsaturated fatty acids" OR "Poria cocos" OR "positive airway pressure" OR "pravastatin" OR "prednisolone" OR "prednisone" OR "prenylflavonoid*" OR "prestarium A" OR "Probenecid" OR "probucol" OR "Prohibitin"

OR "Prolit" OR "propolis" OR "prostaglandin E1" OR "protein restrict*" OR "protocatechuic acid" OR "Psidium guajava" OR "PTRA" OR "Ptx" OR "pulse therapy" OR "Purple corn anthocyanins" OR "pyelolithotomy" OR "pyridoxal" OR "pyridoxamine" OR "pyridoxine" OR "Pyrophosphate" OR "pyrrolidine-dithiocarbamate" OR "Qidi Yiqi Yangyin Huoxue" OR "qingre huoxue" OR "qingshen granule" OR "quercetin" OR "Qufeng Tongluo" OR "quinapril" OR "quinupristin" OR "R-568" OR "rabdosiin" OR "radiation" OR "Radix Astragali" OR "radon therapy" OR "radon water" OR "raloxifene" OR "ramipril" OR "Rapamycin" OR "rasburicase" OR "red wine" OR "reduced glutathione" OR "relaxin" OR "renal angioplasty" OR "renal revascularization" OR "renal transplant" OR "renoureteral catheter" OR "repaglinide" OR "reserpine" OR "Reserpinum Triamterene" OR "resveratrol" OR "retinoic acid" OR "revascularization" OR "rhein" OR "rhEPO" OR "Rheum officinale" OR "Rheum palmatum" OR "Rhizoma Ligustici chuanxiong" OR "rhodamine derivative*" OR "rhubarb" OR "rHuEPO" OR "ribavirin" OR "rice-bran-oil near/3 Tocotrienol-rich-fraction" OR "rifampicin" OR "rifampin" OR "rimonabant" OR "Risedronate" OR "ritanserin" OR "rituximab" OR "RNA interference" OR "rolipram" OR "Rosa laevigata Michx" OR "rosiglitazone" OR "rosmarinic acid" OR "rosuvastatin" OR "rottlerin" OR "R-roscovitine" OR "RS504393" OR "ruboxistaurin" OR "rutin" OR "Saccharomyces boulardii" OR "safflower-seed oil" OR "saikosaponin a" OR "saikosaponin c" OR "saikosaponin d" OR "Saikosaponin-d" OR "Sairei-to" OR "salacia chinensis" OR "salbutamol" OR "salt restrict*" OR "Salvia miltiorrhiza" OR "salvianolate" OR "sandimmun" OR "Sarpogrelate" OR "SAT05f" OR "saxagliptin" OR "SB203580" OR "Schisandra chinensis" OR "selenium" OR "selenomethionine" OR "seliciclib" OR "sevelamer" OR "Shao" OR "Shao Tang" OR "Shathavaryadi Yoga" OR "Shen Yan Ling" OR "Shenkang" OR "Shenkangwan" OR "shenle capsule" OR "shenqi fuzheng" OR "Shenqi Jiedu" OR "shenshuaining" OR "Short interfering RNAs" OR "sialic acid" OR "sildenafil" OR "silymarin" OR "simvastatin" OR "sinusoidal modulated currents" OR "siRNA" OR "sirolimus" OR "sitagliptin" OR "sitaxsentan" OR "Skimmin" OR "skin grafting" OR "SM934" OR "smoking cessation" OR "SMP-534" OR "sodium bicarbonate" OR "sodium chloride bath*" OR "sodium ferulate" OR "sodium polystyrene sulf*" OR "sodium restrict*" OR "sodium selenite" OR "sodium thiosulfate" OR "somatostatin" OR "soy isoflavones" OR "soy protein" OR "sparflo" OR "sparfloxacin" OR "spirapril" OR "spironolactone" OR "Spirulina platensis" OR "SR141716" OR "stanniocalcin-1" OR "stavudine" OR "stent implantation" OR "Sulfasalazine" OR "sulfonylurea" OR "sulforaphane" OR "sulfur amino acid" OR "sulodexide" OR "sulphated hyaluronic acid" OR "suramin" OR "surgical revascularization" OR "T-1095" OR "TA606" OR "Tabanus fulvus Meigan" OR "tacrolimus" OR "tamoxifen" OR "Tang" OR "Tangshenning" OR "Tangshenqing" OR "Tanshinone IIA" OR "taurine" OR "TCM-WM" OR "teicoplanin" OR "telmisartan" OR "temocapril" OR "Tempol" OR "Tenofovir" OR "Terazosin Hydrochloride" OR "terlipressin" OR "Testosterone" OR "TETA" OR "Tetrahydrocurcumin" OR "Tetrahydroxystilbene glucoside" OR "tetramethylpyrazine" OR "TFPI" OR "thalidomide" OR "theophylline" OR "thiamine" OR "thiazide" OR "Thiazolidinedione" OR "thienam" OR "threonine" OR "thrombomodulin" OR "thymoquinone" OR "thymosin" OR "Thyrotropin" OR "TIAOJINING" OR "tissue engineering" OR "TJN-331 " OR "TJN-598" OR "Tocilizumab" OR "tolvaptan" OR "Tongluo" OR "torasemide" OR "TRAM-34" OR "tramadol" OR "Trandolapril" OR "Tranexamic acid" OR "Tranilast" OR "transfer factor" OR "transluminal angioplasty" OR "Triamcinolone acetonide" OR "trichostatin A" OR "triethylenetetramine" OR "trimethoprim-sulfamethoxazole" OR "Tripterygium wilfordii Hook" OR "triptolide" OR "troglitazone" OR "turmeric" OR "U-0126" OR "ultrasound" OR "ultraviolet B" OR "Ultravist" OR "unfractionated heparin" OR "Urate oxidase" OR "urinary alkalinization" OR "uroguanylin" OR "urokinase" OR "Uroprofit" OR "Ursodeoxycholic acid" OR "UVB" OR "valproate" OR "valproic acid"

OR "valsartan" OR "vanadium-lazaroid" OR "Vancomycin" OR "vascular endothelial growth factor" OR "VDRA" OR "vegan diet*" OR "vegetable proteins" OR "vegetarian" OR "VEGF" OR "Venlafaxine" OR "venom" OR "verapamil" OR "vessel revascularization" OR "vildagliptin" OR "Vincristine" OR "vitamin B6" OR "vitamin C" OR "vitamin D" OR "vitamin D3" OR "vitamin E" OR "Vitamin K" OR "VKA" OR "voriconazole" OR "walking" OR "Wang Kentang's Bai Fu Ling Wan" OR "warfarin" OR "wen-pi-tang" OR "Wenshen Huatan" OR "wenshen xiezhuo" OR "xiaochalhu" OR "Xiezhuo" OR "Xueshuantong" OR "Y-27632" OR "yiqi zishen" OR "Yishen Huoxue" OR "yishen jianpi huayu" OR "Zinc" OR "Zingiber officinale Roscoe" OR "zishen huayu fang"

(core literature-derived CKD treatments that were too general and might have eliminated specific discoveries in the same class were subtracted from this negation term: "corticoid*" OR "dairy" OR "exercise" OR "fatty acid*" OR "fish" OR "fruit*" OR "iron" OR "lanthanum" OR "phototherapy" OR "phytochemicals" OR "seeds" OR "soy" OR "tea" OR "tocopherols" OR "vegetables")

AND

2. **TITLE PHRASES - (excludes dialysis and transplantation)**

2a. (treat* OR therap* OR cure* OR intervention* OR rehabilitat* OR monotherap* OR pretreat* OR psychotherap* OR pharmacotherap* OR medication* OR drug* OR stimulant* OR pharmacological* OR diet* OR supplementation OR protect* OR alleviate* OR ameliorate* OR improv* OR benefit* OR reduc* OR inhibit* OR decreas* OR prevent* OR suppress* OR lessen* OR lower* OR mitigat*) near/5 (glycat* OR "peripheral vascular disease" OR arteriosclerosis OR vasoconstriction OR glycosylat* OR endothelin-1 OR inflammation OR hypertension OR "insulin resistance" OR fibrosis OR "metabolic syndrome" OR hyperglycemia OR nephropathy OR fibrogenesis OR "arterial stiffness")

NOT

2b. (glycat*-reduc* OR glycat*-inhibit* OR glycat*-decreas* OR glycat*-prevent* OR glycat*-suppress* OR glycat*-lessen* OR glycat*-lower* OR glycat*-mitigat* OR "glycat* caus*" OR "caused by glycat*" OR "glycat* induc*" OR "induced by glycat*" OR "glycat* was due to" OR "glycat* due to" OR "lead* to glycat*" OR "result* in glycat*" OR "role in glycat*" OR "glycat* was produced by" OR "glycat* produced by" OR "role in glycat*" OR "glycat* provoked by" OR "glycat* was provoked by" OR "provoked glycat*" OR "produce* glycat*" OR "glycat* was produced by" OR "incidence of glycat*" OR "incident glycat*" OR "getting glycat*" OR "prevalence of glycat*" OR "susceptib* to glycat*" OR "contribut* to glycat*" OR "development of glycat*" OR "develop* glycat*" OR "aggravat* glycat*" OR "resulted in glycat*") OR ("peripheral vascular disease reduc*" OR "peripheral vascular disease inhibit*" OR "peripheral vascular disease decreas*" OR "peripheral vascular disease prevent*" OR "peripheral vascular disease suppress*" OR "peripheral vascular disease lessen*" OR "peripheral vascular disease lower*" OR "peripheral vascular disease mitigat*" OR "peripheral vascular disease caus*" OR "caused by peripheral vascular disease" OR "peripheral vascular disease induc*" OR "induced by peripheral vascular disease" OR "peripheral vascular disease was due to" OR "peripheral vascular disease due to" OR "lead* to peripheral vascular disease" OR "result* in peripheral vascular disease" OR "role in peripheral vascular disease" OR "peripheral vascular disease was produced by" OR "peripheral vascular disease produced by" OR "role in peripheral vascular disease" OR "peripheral vascular disease provoked by" OR "peripheral vascular disease was provoked by" OR "provoked peripheral vascular disease" OR "produce*

peripheral vascular disease" OR "peripheral vascular disease was produced by" OR "incidence of peripheral vascular disease" OR "incident peripheral vascular disease" OR "getting peripheral vascular disease" OR "prevalence of peripheral vascular disease" OR "susceptib* to peripheral vascular disease" OR "contribut* to peripheral vascular disease" OR "development of peripheral vascular disease" OR "develop* peripheral vascular disease" OR "aggravat* peripheral vascular disease" OR "resulted in peripheral vascular disease") OR (arteriosclerosis-reduc* OR arteriosclerosis-inhibit* OR arteriosclerosis-decreas* OR arteriosclerosis-prevent* OR arteriosclerosis-suppress* OR arteriosclerosis-lessen* OR arteriosclerosis-lower* OR arteriosclerosis-mitigat* OR "arteriosclerosis caus*" OR "caused by arteriosclerosis" OR "arteriosclerosis induc*" OR "induced by arteriosclerosis" OR "arteriosclerosis was due to" OR "arteriosclerosis due to" OR "lead* to arteriosclerosis" OR "result* in arteriosclerosis" OR "role in arteriosclerosis" OR "arteriosclerosis was produced by" OR "arteriosclerosis produced by" OR "role in arteriosclerosis" OR "arteriosclerosis provoked by" OR "arteriosclerosis was provoked by" OR "provoked arteriosclerosis" OR "produce* arteriosclerosis" OR "arteriosclerosis was produced by" OR "incidence of arteriosclerosis" OR "incident arteriosclerosis" OR "getting arteriosclerosis" OR "prevalence of arteriosclerosis" OR "susceptib* to arteriosclerosis" OR "contribut* to arteriosclerosis" OR "development of arteriosclerosis" OR "develop* arteriosclerosis" OR "aggravat* arteriosclerosis" OR "resulted in arteriosclerosis")

OR

(vasoconstriction-reduc* OR vasoconstriction-inhibit* OR vasoconstriction-decreas* OR vasoconstriction-prevent* OR vasoconstriction-suppress* OR vasoconstriction-lessen* OR vasoconstriction-lower* OR vasoconstriction-mitigat* OR "vasoconstriction caus*" OR "caused by vasoconstriction" OR "vasoconstriction induc*" OR "induced by vasoconstriction" OR "vasoconstriction was due to" OR "vasoconstriction due to" OR "lead* to vasoconstriction" OR "result* in vasoconstriction" OR "role in vasoconstriction" OR "vasoconstriction was produced by" OR "vasoconstriction produced by" OR "role in vasoconstriction" OR "vasoconstriction provoked by" OR "vasoconstriction was provoked by" OR "provoked vasoconstriction" OR "produce* vasoconstriction" OR "vasoconstriction was produced by" OR "incidence of vasoconstriction" OR "incident vasoconstriction" OR "getting vasoconstriction" OR "prevalence of vasoconstriction" OR "susceptib* to vasoconstriction" OR "contribut* to vasoconstriction" OR "development of vasoconstriction" OR "develop* vasoconstriction" OR "aggravat* vasoconstriction" OR "resulted in vasoconstriction") OR (glycosylat*-reduc* OR glycosylat*-inhibit* OR glycosylat*-decreas* OR glycosylat*-prevent* OR glycosylat*-suppress* OR glycosylat*-lessen* OR glycosylat*-lower* OR glycosylat*-mitigat* OR "glycosylat* caus*" OR "caused by glycosylat*" OR "glycosylat* induc*" OR "induced by glycosylat*" OR "glycosylat* was due to" OR "glycosylat* due to" OR "lead* to glycosylat*" OR "result* in glycosylat*" OR "role in glycosylat*" OR "glycosylat* was produced by" OR "glycosylat* produced by" OR "role in glycosylat*" OR "glycosylat* provoked by" OR "glycosylat* was provoked by" OR "provoked glycosylat*" OR "produce* glycosylat*" OR "glycosylat* was produced by" OR "incidence of glycosylat*" OR "incident glycosylat*" OR "getting glycosylat*" OR "prevalence of glycosylat*" OR "susceptib* to glycosylat*" OR "contribut* to glycosylat*" OR "development of glycosylat*" OR "develop* glycosylat*" OR "aggravat* glycosylat*" OR "resulted in glycosylat*") OR (endothelin-1-reduc* OR endothelin-1-inhibit* OR endothelin-1-decreas* OR endothelin-1-prevent* OR endothelin-1-suppress* OR endothelin-1-lessen* OR endothelin-1-lower* OR endothelin-1-mitigat* OR "endothelin-1 caus*" OR "caused by endothelin-1" OR "endothelin-1

induc*" OR "induced by endothelin-1" OR "endothelin-1 was due to" OR "endothelin-1 due to" OR "lead* to endothelin-1" OR "result* in endothelin-1" OR "role in endothelin-1" OR "endothelin-1 was produced by" OR "endothelin-1 produced by" OR "role in endothelin-1" OR "endothelin-1 provoked by" OR "endothelin-1 was provoked by" OR "provoked endothelin-1" OR "produce* endothelin-1" OR "endothelin-1 was produced by" OR "incidence of endothelin-1" OR "incident endothelin-1" OR "getting endothelin-1" OR "prevalence of endothelin-1" OR "susceptib* to endothelin-1" OR "contribut* to endothelin-1" OR "development of endothelin-1" OR "develop* endothelin-1" OR "aggravat* endothelin-1" OR "resulted in endothelin-1")

OR

(inflammation-reduc* OR inflammation-inhibit* OR inflammation-decreas* OR inflammation-prevent* OR inflammation-suppress* OR inflammation-lessen* OR inflammation-lower* OR inflammation-mitigat* OR "inflammation caus*" OR "caused by inflammation" OR "inflammation induc*" OR "induced by inflammation" OR "inflammation was due to" OR "inflammation due to" OR "lead* to inflammation" OR "result* in inflammation" OR "role in inflammation" OR "inflammation was produced by" OR "inflammation produced by" OR "role in inflammation" OR "inflammation provoked by" OR "inflammation was provoked by" OR "provoked inflammation" OR "produce* inflammation" OR "inflammation was produced by" OR "incidence of inflammation" OR "incident inflammation" OR "getting inflammation" OR "prevalence of inflammation" OR "susceptib* to inflammation" OR "contribut* to inflammation" OR "development of inflammation" OR "develop* inflammation" OR "aggravat* inflammation" OR "resulted in inflammation") OR (hypertension-reduc* OR hypertension-inhibit* OR hypertension-decreas* OR hypertension-prevent* OR hypertension-suppress* OR hypertension-lessen* OR hypertension-lower* OR hypertension-mitigat* OR "hypertension caus*" OR "caused by hypertension" OR "hypertension induc*" OR "induced by hypertension" OR "hypertension was due to" OR "hypertension due to" OR "lead* to hypertension" OR "result* in hypertension" OR "role in hypertension" OR "hypertension was produced by" OR "hypertension produced by" OR "role in hypertension" OR "hypertension provoked by" OR "hypertension was provoked by" OR "provoked hypertension" OR "produce* hypertension" OR "hypertension was produced by" OR "incidence of hypertension" OR "incident hypertension" OR "getting hypertension" OR "prevalence of hypertension" OR "susceptib* to hypertension" OR "contribut* to hypertension" OR "development of hypertension" OR "develop* hypertension" OR "aggravat* hypertension" OR "resulted in hypertension") OR ("insulin resistance reduc*" OR "insulin resistance inhibit*" OR "insulin resistance decreas*" OR "insulin resistance prevent*" OR "insulin resistance suppress*" OR "insulin resistance lessen*" OR "insulin resistance lower*" OR "insulin resistance mitigat*" OR "insulin resistance caus*" OR "caused by insulin resistance" OR "insulin resistance induc*" OR "induced by insulin resistance" OR "insulin resistance was due to" OR "insulin resistance due to" OR "lead* to insulin resistance" OR "result* in insulin resistance" OR "role in insulin resistance" OR "insulin resistance was produced by" OR "insulin resistance produced by" OR "role in insulin resistance" OR "insulin resistance provoked by" OR "insulin resistance was provoked by" OR "provoked insulin resistance" OR "produce* insulin resistance" OR "insulin resistance was produced by" OR "incidence of insulin resistance" OR "incident insulin resistance" OR "getting insulin resistance" OR "prevalence of insulin resistance" OR "susceptib* to insulin resistance" OR "contribut* to insulin resistance" OR "development of insulin resistance" OR "develop* insulin resistance" OR "aggravat* insulin resistance" OR "resulted in insulin resistance")

OR

(fibrosis-reduc* OR fibrosis-inhibit* OR fibrosis-decreas* OR fibrosis-prevent* OR fibrosis-suppress* OR fibrosis-lessen* OR fibrosis-lower* OR fibrosis-mitigat* OR "fibrosis caus*" OR "caused by fibrosis" OR "fibrosis induc*" OR "induced by fibrosis" OR "fibrosis was due to" OR "fibrosis due to" OR "lead* to fibrosis" OR "result* in fibrosis" OR "role in fibrosis" OR "fibrosis was produced by" OR "fibrosis produced by" OR "role in fibrosis" OR "fibrosis provoked by" OR "fibrosis was provoked by" OR "provoked fibrosis" OR "produce* fibrosis" OR "fibrosis was produced by" OR "incidence of fibrosis" OR "incident fibrosis" OR "getting fibrosis" OR "prevalence of fibrosis" OR "susceptib* to fibrosis" OR "contribut* to fibrosis" OR "development of fibrosis" OR "develop* fibrosis" OR "aggravat* fibrosis" OR "resulted in fibrosis") OR ("metabolic syndrome reduc*" OR "metabolic syndrome inhibit*" OR "metabolic syndrome decreas*" OR "metabolic syndrome prevent*" OR "metabolic syndrome suppress*" OR "metabolic syndrome lessen*" OR "metabolic syndrome lower*" OR "metabolic syndrome mitigat*" OR "metabolic syndrome caus*" OR "caused by metabolic syndrome" OR "metabolic syndrome induc*" OR "induced by metabolic syndrome" OR "metabolic syndrome was due to" OR "metabolic syndrome due to" OR "lead* to metabolic syndrome" OR "result* in metabolic syndrome" OR "role in metabolic syndrome" OR "metabolic syndrome was produced by" OR "metabolic syndrome produced by" OR "role in metabolic syndrome" OR "metabolic syndrome provoked by" OR "metabolic syndrome was provoked by" OR "provoked metabolic syndrome" OR "produce* metabolic syndrome" OR "metabolic syndrome was produced by" OR "incidence of metabolic syndrome" OR "incident metabolic syndrome" OR "getting metabolic syndrome" OR "prevalence of metabolic syndrome" OR "susceptib* to metabolic syndrome" OR "contribut* to metabolic syndrome" OR "development of metabolic syndrome" OR "develop* metabolic syndrome" OR "aggravat* metabolic syndrome" OR "resulted in metabolic syndrome") OR (hyperglycemia-reduc* OR hyperglycemia-inhibit* OR hyperglycemia-decreas* OR hyperglycemia-prevent* OR hyperglycemia-suppress* OR hyperglycemia-lessen* OR hyperglycemia-lower* OR hyperglycemia-mitigat* OR "hyperglycemia caus*" OR "caused by hyperglycemia" OR "hyperglycemia induc*" OR "induced by hyperglycemia" OR "hyperglycemia was due to" OR "hyperglycemia due to" OR "lead* to hyperglycemia" OR "result* in hyperglycemia" OR "role in hyperglycemia" OR "hyperglycemia was produced by" OR "hyperglycemia produced by" OR "role in hyperglycemia" OR "hyperglycemia provoked by" OR "hyperglycemia was provoked by" OR "provoked hyperglycemia" OR "produce* hyperglycemia" OR "hyperglycemia was produced by" OR "incidence of hyperglycemia" OR "incident hyperglycemia" OR "getting hyperglycemia" OR "prevalence of hyperglycemia" OR "susceptib* to hyperglycemia" OR "contribut* to hyperglycemia" OR "development of hyperglycemia" OR "develop* hyperglycemia" OR "aggravat* hyperglycemia" OR "resulted in hyperglycemia")

OR

(nephropathy-reduc* OR nephropathy-inhibit* OR nephropathy-decreas* OR nephropathy-prevent* OR nephropathy-suppress* OR nephropathy-lessen* OR nephropathy-lower* OR nephropathy-mitigat* OR "nephropathy caus*" OR "caused by nephropathy" OR "nephropathy induc*" OR "induced by nephropathy" OR "nephropathy was due to" OR "nephropathy due to" OR "lead* to nephropathy" OR "result* in nephropathy" OR "role in nephropathy" OR "nephropathy was produced by" OR "nephropathy produced by" OR "role in nephropathy" OR "nephropathy provoked by" OR "nephropathy was provoked by" OR "provoked nephropathy" OR "produce* nephropathy" OR "nephropathy was

produced by" OR "incidence of nephropathy" OR "incident nephropathy" OR "getting nephropathy" OR "prevalence of nephropathy" OR "susceptib* to nephropathy" OR "contribut* to nephropathy" OR "development of nephropathy" OR "develop* nephropathy" OR "aggravat* nephropathy" OR "resulted in nephropathy") OR (fibrogenesis-reduc* OR fibrogenesis-inhibit* OR fibrogenesis-decreas* OR fibrogenesis-prevent* OR fibrogenesis-suppress* OR fibrogenesis-lessen* OR fibrogenesis-lower* OR fibrogenesis-mitigat* OR "fibrogenesis caus*" OR "caused by fibrogenesis" OR "fibrogenesis induc*" OR "induced by fibrogenesis" OR "fibrogenesis was due to" OR "fibrogenesis due to" OR "lead* to fibrogenesis" OR "result* in fibrogenesis" OR "role in fibrogenesis" OR "fibrogenesis was produced by" OR "fibrogenesis produced by" OR "role in fibrogenesis" OR "fibrogenesis provoked by" OR "fibrogenesis was provoked by" OR "provoked fibrogenesis" OR "produce* fibrogenesis" OR "fibrogenesis was produced by" OR "incidence of fibrogenesis" OR "incident fibrogenesis" OR "getting fibrogenesis" OR "prevalence of fibrogenesis" OR "susceptib* to fibrogenesis" OR "contribut* to fibrogenesis" OR "development of fibrogenesis" OR "develop* fibrogenesis" OR "aggravat* fibrogenesis" OR "resulted in fibrogenesis") OR ("arterial stiffness reduc*" OR "arterial stiffness inhibit*" OR "arterial stiffness decreas*" OR "arterial stiffness prevent*" OR "arterial stiffness suppress*" OR "arterial stiffness lessen*" OR "arterial stiffness lower*" OR "arterial stiffness mitigat*" OR "arterial stiffness caus*" OR "caused by arterial stiffness" OR "arterial stiffness induc*" OR "induced by arterial stiffness" OR "arterial stiffness was due to" OR "arterial stiffness due to" OR "lead* to arterial stiffness" OR "result* in arterial stiffness" OR "role in arterial stiffness" OR "arterial stiffness was produced by" OR "arterial stiffness produced by" OR "role in arterial stiffness" OR "arterial stiffness provoked by" OR "arterial stiffness was provoked by" OR "provoked arterial stiffness" OR "produce* arterial stiffness" OR "arterial stiffness was produced by" OR "incidence of arterial stiffness" OR "incident arterial stiffness" OR "getting arterial stiffness" OR "prevalence of arterial stiffness" OR "susceptib* to arterial stiffness" OR "contribut* to arterial stiffness" OR "development of arterial stiffness" OR "develop* arterial stiffness" OR "aggravat* arterial stiffness" OR "resulted in arterial stiffness") - title

OR (based on treatment MeSH terms)

2c. ("Adrenergic alpha-1 Receptor Antagonist*" OR "Adrenergic beta-Agonist*" OR "Adrenergic beta-Antagonist*" OR "Aldosterone Antagonist*" OR "Essential Amino Acid*" OR "Anabolic Agent*" OR "Androgen*" OR "Angiotensin II Type 1 Receptor Blockers*" OR "Angiotensin II Type 2 Receptor Blockers*" OR "Angiotensin Receptor Antagonist*" OR "Angiotensin-Converting Enzyme Inhibitor*" OR "Anti-Arrhythmia Agent*" OR "Monoclonal Antibodies" OR "Anticholesteremic Agent*" OR "Anticoagulant*" OR "Antifibrinolytic Agent*" OR "Antihypertensive*" OR "Anti-Inflammatory Agent*" OR "Antioxidant*" OR "Antithrombin*" OR "Antitubercular Agent*" OR "Anti-Ulcer Agent*" OR "Biological Availability" OR "Biosimilar Pharmaceutical*" OR "Blood Substitute*" OR "Bone Density Conservation Agent*" OR "Bone Morphogenetic Protein*" OR "Calcimimetic Agent*" OR "Calcium Channel Agonist*" OR "Calcium Channel Blocker*" OR "Caloric Restriction" OR "Cardiotonic Agent*" OR "Cardiovascular Agent*" OR "Chelating Agent*" OR "Colony-Stimulating Factor*" OR "Combined Modality Therapy" OR "Complement Inactivating Agent*" OR "Complement Inactivator Protein*" OR "Complementary Therap*" OR "Condiment*" OR "Cyclooxygenase Inhibitor*" OR "Cytoprotection" OR "Diabetic Diet*" OR "Diet Therap*" OR "Carbohydrate-Restricted diet*" OR "Fat-Restricted Diet*" OR "Mediterranean Diet*" OR "Protein-Restricted Diet*" OR "Sodium-Restricted Diet*" OR "Vegetarian Diet*" OR "Dietary Carbohydrates" OR "Dietary Fat*" OR "Dietary Fiber" OR "Dietary Protein*" OR

"Dietary Supplement*" OR "Dietetics" OR "Dipeptidyl-Peptidase IV Inhibitor*" OR "Dose-Response Relationship*" OR "Drug Combination*" OR "Drug Discovery" OR "Drug Evaluation" OR "Drug Synergism" OR "Drug Therapy" OR "Drug Therapy" OR "Drug Utilization" OR "Investigational Drugs" OR "Embryonic Stem Cell*" OR "Energy Intake" OR "Enzyme Inhibitor*" OR "Estrogen*" OR "Exercise Therapy" OR "Fermentation" OR "Fetal Stem Cell*" OR "Fibrinolytic Agent*" OR "Flavonoid*" OR "Food Handling" OR "Formulated Food" OR "Free Radical Scavenger*" OR "Fruit*" OR "Gastrointestinal Agent*" OR "Gene Expression Regulation" OR "Gene Therapy" OR "Genetic Vector*" OR "Glycosaminoglycan*" OR "Health Food*" OR "Hematopoietic Stem Cell*" OR "Hirudin Therapy" OR "Horme*" OR "Human Growth Hormone*" OR "Hydroxymethylglutaryl-CoA Reductase Inhibitor*" OR "Hypoglycemic Agent*" OR "Hypolipidemic Agent*" OR "Inflammation Mediator*" OR "Integrative Medicine" OR "Isoflavone*" OR "Leukotriene Antagonist*" OR "Chinese Traditional Medicine" OR "Traditional Medicine" OR "Mesenchymal Stem Cell*" OR "Micronutrient*" OR "Motor Activity" OR "Multipotent Stem Cell*" OR "Neuroprotective Agent*" OR "Nonprescription Drug*" OR "Nutrition Policy" OR "Nutrition Therapy" OR "Nutritional Physiological Phenomena" OR "Nutritional Requirement*" OR "Nutritional Science*" OR "Nutritional Support" OR "Parenteral Nutrition" OR "Peripheral Blood Stem Cell*" OR "Pharmaceutical Preparation*" OR "Pharmacokinetic*" OR "Phenol*" OR "Phosphodiesterase 5 Inhibitor*" OR "Phosphodiesterase Inhibitor*" OR "Phytoestrogen*" OR "Phytotherapy" OR "Plant Extract*" OR "Plant Leaves" OR "Plant Oil*" OR "Plant Preparation*" OR "Plant Protein*" OR "Plant Root*" OR "Medicinal Plant*" OR "Platelet Aggregation Inhibitor*" OR "Pluripotent Stem Cell*" OR "Polyphenol*" OR "Prebiotic*" OR "Prescription Drug*" OR "Primary Prevention" OR "Probiotic*" OR "Protease Inhibitor*" OR "Protective Agent*" OR "Protein Kinase Inhibitor*" OR "Recombinant Protein*" OR "Regeneration" OR "Seed*" OR "Selective Estrogen Receptor Modulator*" OR "Sodium Chloride Symporter Inhibitor*" OR "Sodium Potassium Chloride Symporter Inhibitor*" OR "Stem Cell Transplantation" OR "Stem Cell*" OR "Steroid*" OR "Stromal Cell*" OR "Synbiotic*" OR "Thrombolytic Therapy" OR "Tissue Therapy" OR "Treatment Outcome" OR "Vasodilator Agent*" OR "Vegetable Protein*" OR "Vegetable*") near/15 (glycat* OR "peripheral vascular disease" OR arteriosclerosis OR vasoconstriction OR glycosylat* OR endothelin-1 OR inflammation OR hypertension OR "insulin resistance" OR fibrosis OR "metabolic syndrome" OR hyperglycemia OR nephropathy OR fibrogenesis OR "arterial stiffness") - **title**

3. **MESH QUALIFIERS - MESH HEADING**

3a. (/diet therapy OR /drug therapy OR /prevention & control OR /radiotherapy OR /rehabilitation OR /therapeutic use OR /therapy OR /administration & dosage OR /pharmacology) - MeSH Heading

AND

3b. (treat* OR therap* OR cure* OR intervention* OR rehabilitat* OR monotherap* OR pretreat* OR psychotherap* OR pharmacotherap* OR medication* OR drug* OR stimulant* OR pharmacological* OR diet* OR supplementation OR protect* OR alleviate* OR ameliorate* OR improv* OR benefit* OR reduc* OR inhibit* OR decreas* OR prevent* OR suppress* OR lessen OR lower* OR mitigat*) - title

OR

4. **MESH GENERIC TERMS - MESH HEADING NO EXPLODE**

(Extracted from 441 Treatment MeSH terms of CKD core analysis, with some related additions)

4a. (Adrenergic alpha-1 Receptor Antagonists OR Adrenergic beta-Agonists OR Adrenergic beta-Antagonists OR Aldosterone Antagonists OR Amino Acids OR Amino Acids, Essential OR Anabolic Agents OR Androgens OR Angiotensin II Type 1 Receptor Blockers OR Angiotensin II Type 2 Receptor Blockers OR Angiotensin Receptor Antagonists OR Angiotensin-Converting Enzyme Inhibitors OR Anti-Arrhythmia Agents OR Antibodies, Monoclonal OR Anticholesteremic Agents OR Anticoagulants OR Antifibrinolytic Agents OR Antihypertensive Agents OR Anti-Inflammatory Agents OR Anti-Inflammatory Agents, Non-Steroidal OR Antioxidants OR Antithrombins OR Antitubercular Agents OR Anti-Ulcer Agents OR Biological Availability OR Biosimilar Pharmaceuticals OR Blood Substitutes OR Bone Density Conservation Agents OR Bone Morphogenetic Proteins OR Calcimimetic Agents OR Calcium Channel Agonists OR Calcium Channel Blockers OR Caloric Restriction OR Cardiotonic Agents OR Cardiovascular Agents OR Chelating Agents OR Colony-Stimulating Factors OR Combined Modality Therapy OR Complement Inactivating Agents OR Complement Inactivator Proteins OR Complementary Therapies OR Condiments OR Cyclooxygenase Inhibitors OR Cytoprotection OR Diabetic Diet OR Diet OR Diet Therapy OR Diet, Carbohydrate-Restricted OR Diet, Fat-Restricted OR Diet, Mediterranean OR Diet, Protein-Restricted OR Diet, Sodium-Restricted OR Diet, Vegetarian OR Dietary Carbohydrates OR Dietary Fats OR Dietary Fats, Unsaturated OR Dietary Fiber OR Dietary Proteins OR Dietary Supplements OR Dietetics OR Dipeptidyl-Peptidase IV Inhibitors OR Dose-Response Relationship, Drug OR Drug Combinations OR Drug Discovery OR Drug Evaluation, Preclinical OR Drug Synergism OR Drug Therapy OR Drug Therapy, Combination OR Drug Utilization OR Drugs, Investigational OR Embryonic Stem Cells OR Energy Intake OR Enzyme Inhibitors OR Estrogens OR Estrogens, Conjugated (USP) OR Estrogens, Non-Steroidal OR Exercise OR Exercise Therapy OR Fermentation OR Fetal Stem Cells OR Fibrinolytic Agents OR Flavonoids OR Food OR Food Handling OR Food, Formulated OR Free Radical Scavengers OR Fruit OR Gastrointestinal Agents OR Gene Expression Regulation OR Gene Therapy OR Genetic Vectors OR Glycosaminoglycans OR Health Food OR Hematopoietic Stem Cell Transplantation OR Hematopoietic Stem Cells OR Hirudin Therapy OR Hirudins OR Hormesis OR Human Growth Hormone OR Hydroxymethylglutaryl-CoA Reductase Inhibitors OR Hypoglycemic Agents OR Hypolipidemic Agents OR Inflammation Mediators OR Integrative Medicine OR Isoflavones OR Leukotriene Antagonists OR Medicine, Chinese Traditional OR Medicine, Traditional OR Mesenchymal Stem Cell Transplantation OR Micronutrients OR Motor Activity OR Multipotent Stem Cells OR Neuroprotective Agents OR Nonprescription Drugs OR Nutrition Policy OR Nutrition Therapy OR Nutritional Physiological Phenomena OR Nutritional Requirements OR Nutritional Sciences OR Nutritional Support OR Parenteral Nutrition OR Peripheral Blood Stem Cell Transplantation OR Pharmaceutical Preparations OR Pharmacokinetics OR Phenols OR Phosphodiesterase 5 Inhibitors OR Phosphodiesterase Inhibitors OR Phytoestrogens OR Phytotherapy OR Plant Extracts OR Plant Leaves OR Plant Oils OR Plant Preparations OR Plant Proteins OR Plant Roots OR Plants, Medicinal OR Platelet Aggregation Inhibitors OR Pluripotent Stem Cells OR Polyphenols OR Prebiotics OR Prescription Drugs OR Primary Prevention OR Probiotics OR Protease Inhibitors OR Protective Agents OR Protein Kinase Inhibitors OR Recombinant Proteins OR Regeneration OR Seeds OR Selective Estrogen Receptor Modulators OR Sodium Chloride Symporter Inhibitors OR Sodium Potassium Chloride Symporter Inhibitors OR Stem Cell Transplantation OR Stem Cells OR Steroids OR Stromal Cells OR Synbiotics OR Thrombolytic Therapy OR Tissue Therapy OR Treatment Outcome OR Vasodilator Agents OR Vegetable Proteins OR Vegetables) - **MeSH Hdg No Expl**

AND

4b. ((treat* OR therap* OR cure* OR intervention* OR rehabilitat* OR monotherap* OR pretreat* OR psychotherap* OR pharmacotherap* OR medication* OR drug* OR stimulant* OR pharmacological* OR diet* OR supplementation OR protect* OR alleviate* OR ameliorate* OR improv* OR benefit* OR reduc* OR inhibit* OR decreas* OR prevent* OR suppress* OR lessen OR lower* OR mitigat*)

About 55 potential Discovery candidates were identified (validated through Medline). Another dozen or so were identified from examining the citation network around some of the 55 initial Discoveries. The next step was validating the 65+ total Discovery candidates through the SCI. A query derived from the MeSH-based query used for CKD was used for the SCI validation:

("chronic kidney disease" OR "chronic kidney failure" OR "chronic renal insufficiency" OR "diabet* near/3 nephropath*" OR nephrosclerosis OR nephrosis OR nephritis)

1D. CKD SYMPTOMS

1D1. Manual generation

The MeSH terms in the full CKD core literature retrieval were examined, and 271 terms related to symptoms were validated and selected. A separate database was generated whose records contained at least one of the symptoms MeSH terms. Tens of thousands of Abstract and title phrases were examined, and those describing a symptom were selected.

1D2. CKD core literature symptoms query

Since the symptoms query was applied only to the CKD core literature to identify any symptoms not identified through the manual process, an abbreviated symptoms query was developed.

Query=((#1a OR #1b) NOT (#1c OR #1d)) AND (#1e OR #1f OR #1g)

1a. ("kidney failure, chronic" OR "renal insufficiency, chronic" OR "Diabetic Nephropathies" OR Nephrosclerosis OR Nephrosis OR Nephritis OR "Nephritis, Interstitial") - **MeSH Heading**

OR

1b. "chronic kidney disease" - **topic**

NOT

1c. (Renal Dialysis OR Kidney Transplantation OR Peritoneal Dialysis OR Peritoneal Dialysis, Continuous Ambulatory OR Nephrectomy OR Transplantation, Homologous OR Graft Rejection OR Graft Survival OR Dialysis Solutions OR Dialysis OR Hemodialysis, Home OR Hemodialysis Solutions OR Hemodialysis Units, Hospital OR Microdialysis OR Transplantation, Autologous OR Transplantation Immunology OR Transplantation Conditioning OR Transplantation, Heterologous OR Delayed Graft Function OR Kidney Neoplasms OR Renal Replacement Therapy OR Pancreas Transplant OR Neoplasms) - **MeSH Heading Field**

OR

(symptom phrases from manual procedure)

1d. (1,25-dihydroxyvitamin D OR 25-hydroxyvitamin D OR 8-hydroxy-2'-deoxyguanosine OR abdominal fat OR adipocytokine* OR ADIPONECTIN OR adipose tissue OR adrenal insufficiency OR advanced glycosylation end products OR adynamic bone OR albumin/creatinine ratio OR albuminuria OR aldosterone OR alkaline phosphatase OR alpha-galactosidase OR alpha-galactosidase A. OR alpha-smooth muscle actin OR amyloidosis OR anaemia OR androgen OR anemia OR angiogenesis OR angiotensin II receptor* OR angiotensin receptor* OR angiotensin-converting enzyme OR ankle-brachial index OR anti-inflamm* OR antioxidant defense OR antiphospholipid syndrome OR Aortic pulse wave velocity OR aplasia OR apolipoprotein* OR apoptosis OR arrhythmias OR arter* stenosis OR arterial stiff* OR arteriosclerosis OR asymmetric dimethylarginine OR atherosclerosis OR atherosclerotic plaques OR azotaemia OR azotemia OR B lymphocytes OR baroreflex OR beta 2-Microglobulin OR beta2-microglobulin OR blood glucose OR blood hemoglobin OR blood pressure OR blood sugar OR blood urea nitrogen OR bone density OR bone mineral density OR cachexia OR calcidiol OR calcification OR

calcinosis OR Calciphylaxis OR calcitonin OR calcium deposition OR calcium oxalate OR calcium phosphate OR carbonyl stress OR carboxymethyllysine OR cardiac hypertrophy OR carnitine OR catalase OR catecholamines OR CD31 OR cGMP OR collagen degradation OR connective tissue growth factor OR copper OR C-reactive protein OR creatine kinase OR dehydration OR dyslipidaemia OR dyslipidemia OR E-cadherin OR edema OR elastin degradation OR endothelin-1 OR erythropoie* OR erythropoietin OR estrogen OR extracellular fluid volume OR extracellular matrix OR extracellular matrix degradation OR extracellular phosphoglycoprotein OR extracellular water OR F2-isoprostanes OR fatty acid synthase OR fatty acid-binding protein* OR FERRITIN OR fetuin-A OR FGF23 OR FGF-23 OR fibrin degradation OR fibrinogen OR fibrinolysis OR fibrinolysis OR fibroblast growth factor 23 OR fibroblast growth factor-23 OR fibrogenesis OR fibrogenic OR fibronectin OR fibrosis OR folate deficiency OR folic acid OR free radicals OR gangrene OR glomerular hypertrophy OR glomerulosclerosis OR glutathione OR glycation OR GLYCATED OR glycemia OR glycosylated hemoglobin OR glycosylation OR glycoxidation OR growth hormone OR haematuria OR haemoglobin OR haploinsufficiency OR heart rate response OR heart rate variability OR hematuria OR hepcidin OR HIGH SERUM CALCIUM OR HIGH SERUM POTASSIUM OR HIGH-DENSITY LIPOPROTEIN OR HDL OR homocysteine OR hydration OR hydrolytic degradation OR hydronephrosis OR hyperaldosteronism OR hypercalcaemi* OR hypercalcemi* OR hypercalciuria OR hypercellularity OR hypercholesterolaemia OR hypercholesterolemi* OR hypercoagulability OR hypercoagulable OR hyperemia OR hyperfiltration OR hyperglycaemia OR hyperglycemi* OR hyperglycosylated OR Hyperhomocysteinaemia OR hyperhomocysteinemi* OR hyperinsulinaemia OR hyperinsulinemi* OR hyperkalaemia OR hyperkalemi* OR hyperleptinemia OR hyperlipid* OR hypermagnesemia OR hyperoxaluria OR hyperparathyroid* OR Hyperphosphataemia OR hyperphosphatemi* OR hyperplasia OR hypersecretion OR hypertens* OR hyperthyroid* OR hypertriglycerid* OR hyperuricaemia OR hyperuricem* OR Hypervolemia OR hypoalbumin* OR hypocalcaemia OR hypocalcemi* OR hypoglycaemia OR hypoglycemi* OR hypogonad* OR hypokalaemia OR hypokalemi* OR hypolipidemi* OR hypomagnesemia OR hypomethylation OR hyponatremia OR hypoparathyroidism OR hypoperfusion OR hypophosphatemi* OR hypoplasia OR hyporespons* OR hypotensi* OR hypothyroid* OR Hypovitaminosis D OR hypoxemia OR hypoxi* OR hypoxia-INDUC* OR hypozincemia OR IFN-gamma OR IL-1* OR IL-18 OR IL-4 OR IL-6 OR IL-8 OR indoxyl sulfate OR inflamm* OR insulin resistance OR insulin sensitivity OR insulin-like growth factor* OR intercellular adhesion molecule-1 OR interferon-gamma OR interleukin-1* OR interleukin-10 OR interleukin-18 OR interleukin-6 OR intima-media thickness OR iron deficiency OR iron depletion OR iron-deficiency OR kallikrein OR Klotho OR lactate dehydrogenase OR lean body mass OR left ventricular ejection fraction OR left ventricular hypertrophy OR left ventricular mass index OR leptin OR leukocyte count OR lipid metabolism OR lipid peroxid* OR lipoperoxidation OR lipotoxicity OR lipoxidation OR LOW SERUM CALCIUM OR LOW SERUM POTASSIUM OR low-density lipoprotein OR LDL OR macroalbuminuria OR macrophage infiltration OR Magnesium OR MG OR Malnutrition OR malondialdehyde OR matrix accumulation OR matrix metalloproteinases OR MDA OR membrane protein DAMAGE OR metabolic acidosis OR metabolic syndrome OR methylenetetrahydrofolate reductase OR methylglyoxal OR methylmalonic OR microalbuminuria OR microinflammation OR mineral metabolism OR mitogen-activated protein KINASE* OR monocyte chemoattractant protein-1 OR myeloperoxidase OR N(epsilon)-(carboxymethyl)lysine OR N-acetyl-beta-D-glucosaminidase OR NADPH oxidase OR natriuretic peptide OR nephrin OR nephrocalcinosis OR nephrogenesis OR nephrogenic fibrosing OR nephron damage OR nephrosclerosis OR neuropeptide Y OR neutrophil gelatinase-associated lipocalin OR NF-kappaB OR

nitric oxide OR nitric oxide synthase OR nonesterified fatty acids OR norepinephrine OR nutrition OR obes* OR oedema OR osteitis fibrosa OR osteocalcin OR osteodystrophy OR osteomalacia OR osteopenia OR osteopontin OR osteoporosis OR osteoprotegerin OR overweight OR oxidation OR oxidative stress OR Oxidized low-density lipoprotein OR pancreatic insufficiency OR paraoxonase OR parathormone OR PARATHORMONE OR parathyroid hormone OR p-cresol OR pentosidine OR peripheral vascular disease OR peroxynitrite OR phospholipid* OR phosphorous OR plasma renin OR Plasmalogens OR plasminogen activator inhibitor OR plasminogen activator inhibitor-1 OR podocyte damage OR podocyte depletion OR profibrotic cytokines OR proinflamm* OR pro-inflamm* OR protein carbonyl* OR protein catabolism OR protein degradation OR protein depletion OR protein excretion OR protein metabolism OR proteinuri* OR pulse wave velocity OR pure red cell aplasia OR pyelonephritis OR reactive oxygen species OR red blood cell* OR renal circulation OR RENAL ISCHEMIA OR Renalase OR retinol-binding protein OR RNA degradation OR SERUM ALBUMIN OR serum amyloid OR serum calcitriol OR serum cholesterol OR serum cTnT OR serum EPO OR SERUM FERRITIN OR serum folate OR serum insulin OR serum lipid* OR serum OPG OR serum parathyroid hormone OR serum phosphate OR serum phosphorus OR serum prealbumin OR Serum sodium OR sleep apnea OR SOX markers Cu/Zn OR spermatogenesis OR superoxide dismutase OR superoxide production OR symmetric dimethylarginine OR sympathetic nerve activity OR Testosterone OR TGF-beta1 OR thyroxine OR TNFalpha OR TNF-alpha OR TRANSFERRIN OR transforming growth factor-beta* OR triglyceride* OR troponin OR tubular atrophy OR tubular necrosis OR tubulointerstitial injury OR tubulointerstitial lesions OR tubulointerstitial nephritis OR tumor necrosis factor* OR type I collagen OR type IV collagen OR tyrosine OR Uraemia OR uremic OR uric acid OR URIN* ALBUMIN OR urin* protein OR URINE albumin-creatinine ratio OR URINE albumin-to-creatinine ratio OR uromodulin OR vascular cell adhesion molecule-1 OR vascular endothelial growth factor OR vascular resistance OR vasculitis OR vasoconstriction OR vasodilatation OR VCAM-1 OR VEGF OR vesicoureteral reflux OR vimentin OR vitamin B12 OR Vitamin C OR vitamin D OR vitamin K OR wall thickness AND (RENAL OR KIDNEY OR ARTERIAL OR VENTRICULAR) OR White blood cell count OR Zinc) - **Topic**

AND

1e. (Signs and Symptoms OR Glomerular Filtration Rate OR Creatinine OR Hypertension OR Biological Markers OR Anemia OR Blood Pressure OR Erythropoietin OR Proteinuria OR Uremia OR Parathyroid Hormone OR Hyperparathyroidism, Secondary OR Calcinosis OR Hemoglobins OR Inflammation OR Oxidative Stress OR C-Reactive Protein OR Albuminuria OR Body Mass Index OR Phosphates OR Phosphorus OR Nutritional Status OR Obesity OR Hypertrophy, Left Ventricular OR Fibrosis OR Urea OR Body Weight OR Arteriosclerosis OR Endothelium, Vascular OR Atherosclerosis OR Hypertension, Renal OR Homocysteine OR Blood Glucose OR Bone Density OR Interleukin-6 OR Blood Urea Nitrogen OR Anemia, Iron-Deficiency OR Cytokines OR Lipids OR Arginine OR Hyperparathyroidism OR Cholesterol OR Malnutrition OR Metabolic Syndrome X OR Insulin Resistance OR Tumor Necrosis Factor-alpha OR Cystatin C OR Hyperlipidemias OR Heart Rate OR Glucose OR Vitamin D Deficiency OR Insulin OR Nitric Oxide OR Hyperphosphatemia OR Body Composition OR Apoptosis OR Triglycerides OR Calciphylaxis OR Potassium OR Ischemia OR Glycosylation End Products, Advanced OR Fibroblast Growth Factors OR Natriuretic Peptide, Brain OR Transforming Growth Factor beta OR Protein-Energy Malnutrition OR Hyperhomocysteinemia OR Hemoglobin A, Glycosylated OR Peptide Fragments OR Dyslipidemias OR Metabolic Clearance Rate OR Hypotension OR Hypercalcemia OR beta 2-Microglobulin OR Stroke

Volume OR Renal Circulation OR Uric Acid OR Hyperkalemia OR Alkaline Phosphatase OR Cholesterol, LDL OR Erythropoiesis OR Transferrin OR Leptin OR Nutrition Disorders OR Acidosis OR Cholesterol, HDL OR Vascular Resistance OR Osteoporosis OR Lipid Peroxidation OR Reactive Oxygen Species OR Lipoproteins, LDL OR Troponin T OR Malondialdehyde OR Nitric Oxide Synthase OR Membrane Proteins OR Bone Remodeling OR Lipoproteins OR Hematuria OR Hypercholesterolemia OR Adiponectin OR Minerals OR Aldosterone OR Adipose Tissue OR Hyperuricemia OR Magnesium OR Superoxide Dismutase OR Albumins OR Cystatins OR Endothelin-1 OR Hyperplasia OR Sleep Disorders OR Cognition Disorders OR Hypocalcemia OR Phosphorus Metabolism Disorders OR Vasculitis OR Troponin I OR Nitric Oxide Synthase Type III OR Phosphorus, Dietary OR Sleep Apnea Syndromes OR Hypertension, Renovascular OR Lipid Metabolism OR Nephrosclerosis OR Fibrinogen OR Elasticity OR Glutathione OR Hyperglycemia OR Hyperoxaluria, Primary OR Edema OR Indican OR Lipoproteins, HDL OR Bone Resorption OR Leukocyte Count OR Extracellular Matrix OR Interleukin-10 OR Interleukin-1 OR Collagen Type I OR NF-kappa B OR Oxygen OR Lipocalins OR Lipoprotein(a) OR Osteoprotegerin OR Lymphocytes OR Norepinephrine OR Restless Legs Syndrome OR Atrial Natriuretic Factor OR Calcifediol OR Plasminogen Activator Inhibitor 1 OR Vascular Calcification OR Glycoproteins OR Testosterone OR Hypoalbuminemia OR Interferon-gamma OR Zinc OR Calcification, Physiologic OR Calcium Phosphates OR Muscular Atrophy OR Creatine Kinase OR Hypophosphatemia OR Hypothyroidism OR Glucose Tolerance Test OR Apolipoproteins OR Apolipoproteins B OR Cachexia OR Methylenetetrahydrofolate Reductase (NADPH2) OR Genetic Markers OR Sleep OR Apolipoproteins E OR Calcitonin OR Hypertension, Pulmonary OR Muscle Proteins OR Sleep Apnea, Obstructive OR Obesity, Morbid OR Nephrocalcinosis OR Uromodulin OR Ankle Brachial Index OR Hypertrophy OR Overweight OR Pulmonary Edema OR Rhabdomyolysis OR Genome-Wide Association Study OR Matrix Metalloproteinase 2 OR NADPH Oxidase OR Antiphospholipid Syndrome OR Anorexia OR Fibronectins OR Appetite OR B-Lymphocytes OR Hyperthyroidism OR Hypokalemia OR Vascular Stiffness OR Catalase OR Glycosylation OR Troponin OR Tyrosine OR Fatty Acid-Binding Proteins OR Hemostasis OR Hypertriglyceridemia OR Angiotensinogen OR Vasoconstriction OR Matrix Metalloproteinase 9 OR Nitrites OR Thyroxine OR Wasting Syndrome OR DNA Damage OR Blood Cell Count OR Calcium Oxalate OR Hyperoxaluria OR Cresols OR Hypoparathyroidism OR Superoxides OR Glucose Intolerance OR Interleukin-8 OR Methylmalonic Acid OR Sulfhydryl Compounds OR Fibrinolysis OR Copper OR Deoxyguanosine OR Phospholipids OR Erythrocyte Count OR Hyperinsulinism OR Hyponatremia OR Acetylglucosaminidase OR Anemia, Hypochromic OR Hyperaldosteronism OR Waist Circumference OR Intra-Abdominal Fat OR Azotemia OR Connective Tissue Growth Factor OR Interleukin-18 OR Lipid Peroxides OR Protein Carbonylation OR Neuropeptide Y OR Nitric Oxide Synthase Type I OR Retinol-Binding Proteins OR F2-Isoprostanes OR Monoamine Oxidase) - **MeSH Heading**

OR

1f. /deficiency - **MeSH Heading**

OR

1g. (biomarker* OR "biological marker*" OR disorder* OR deficien* OR deplet* OR associat* OR risk* OR "surrogate marker*" OR "metabolic profile*" OR profiling OR abnormal* OR insufficien* OR dysfunction* OR impair* OR poor OR hypo* OR degrad* OR dysregulat*OR deteriorat* OR deficit* OR

defect* OR disturb* OR susceptib* OR instability OR (plasma OR serum OR blood OR hemoglobin) near/3 (level* OR concentration*) OR link* OR indicat* OR predict*) - Topic

(return to TOC)

APPENDIX 2 – PERVASIVE CAUSES OF DISEASE CONTRIBUTING FACTOR IDENTIFICATION METHODOLOGY

1B. Methodology used to Retrieve Causes-Related Articles

1B1. Identification of Causes of Disease

The present study focuses on identifying all direct and indirect foundational causes for all diseases and symptoms. It extrapolates, and significantly advances, the techniques used in our recent study on causes (and treatments) of a single disease, chronic kidney disease (CKD), in which approximately 900 direct and indirect causes of CKD were identified [12]. The goal is to present a quasi-streamlined methodology for identifying the full spectrum of potential causes, and relating them to the full spectrum of diseases and symptoms. Expanding single-disease queries developed in past studies (such as [12]) to all diseases and symptoms is not practical because of the sheer magnitude of query terms required.

Three approaches were used: one highly streamlined, and two far less streamlined. The highly streamlined approach used MeSH Qualifiers only to retrieve the records for analysis. The first of the less streamlined approaches used generic MeSH terms relatively unamibiguously related to causes to retrieve the records for analysis, and the second of the less streamlined approaches used text terms applied to the Title field to retrieve the records. The results of all three approaches were integrated in the main body of the text; the details of the approaches follow.

1B1a. MeSH Qualifiers Approach

1B1a1. MeSH Format Causes

An offshoot of the MeSH Qualifier concept was used for identifying causes. There are 83 topical MeSH Qualifiers used for indexing and cataloging in conjunction with MeSH Heading descriptors. All 83 were examined in more or less detail for applicability to identifying foundational causes of disease. Four were selected as producing highly relevant results: **adverse effects, toxicity, pathogenicity, poisoning**. A few limited combinations of the remaining Qualifiers were examined, but none were deemed to have sufficient relevance. These four Qualifiers constituted the query.

It was decided to use Pubmed as the source search engine for the Medline database rather than Thomson Medline, as was used in the CKD study [12]. Much larger retrievals were expected in the present study because of the numbers of causes and diseases expected. In Pubmed, the full retrieval can be downloaded at once; in Thompson, only 500 records per download are allowed. When downloading hundreds of thousands of records, download time becomes important. Also, Pubmed introduces records at an earlier stage of processing. For example, a search of Thomson for 'virus' in the Title for 2014 (performed on 19 May 2014) retrieved 3789 records, whereas a search of Pubmed with the same query retrieved 4951 records. For the above reasons, and since the proximity search capability of Thomson would not be used for this study, Pubmed was used as the data source.

This simplified query (consisting of four MeSH Qualifiers) was entered into Pubmed for the time interval 2004-2014, 592,074 records (all with Abstracts) were retrieved and downloaded on 10 May 2014, and were imported into the Vantage Point software. 591,884 unique Abstracts were displayed by the software. There were 595,730 MeSH terms (with Qualifiers) listed. All MeSH terms that included at

least one of the above four Qualifiers were placed in a separate group, containing a total of 116,538 MeSH terms with Qualifiers. The software integrated over the MeSH Qualifiers to yield 9,038 MeSH Headings (no Qualifiers shown). These were the foundational causes for all diseases expressed in MeSH terminology.

It was desired to generate a causes-diseases and symptoms matrix. Therefore, the diseases and symptoms needed to be identified and grouped. A detailed examination of the remaining Qualifiers, and observation of Qualifier patterns in the records where causes Qualifiers appeared, showed that the following Qualifiers tended to be associated with diseases and symptoms: etiology, chemically induced, complications, pathology, diagnosis, immunology, microbiology, parasitology, physiopathology, virology, epidemiology, radiation effects, metabolism, drug effects, prevention and control. All MeSH terms that included at least one of the above fifteen Qualifiers were placed in a separate group, containing a total of 353,383 MeSH terms with Qualifiers. The software integrated over the MeSH Qualifiers to yield 17,142 MeSH Headings (no Qualifiers shown).

However, this initial list went beyond diseases and symptoms, and required further filtering. NIH generates a Web site entitled MeSH Tree Structures (http://www.nlm.nih.gov/mesh/trees.html) that lists all the MeSH Headings in the different branches of the MeSH tree. The MeSH Headings listed for all diseases and symptoms were downloaded and intersected with the above list of 17,142 MeSH Headings. A perusal of this filtered list, compared with the unfiltered list, showed a number of items that were not listed in the MeSH tree under one of the three categories, but, nevertheless, were impacted by the items listed as 'causes'. For the most part, these additional items could be viewed as processes and mechanisms. Therefore, the first 5,000 items in the list of 17,142 MeSH Headings were inspected visually, and all those that could be impacted by the 'causes' were added to the filtered list. Substantial sampling was performed to validate any selections in question. The resulting list of 5,870 diseases and symptoms was inspected visually, and any terms that were not diseases or symptoms (typically biomarkers) were removed. There were 4,147 diseases in the final list.

It became clear at this point that two different matrices would be preferable for identifying direct foundational causes and indirect foundational causes. For identifying and tabulating direct causes, a causes-diseases and symptoms matrix would offer the most credibility. For identifying indirect causes, a causes-diseases and symptoms matrix linked to a diseases and symptoms square matrix would be preferable, because causes could then be linked to the disease(s) of interest through other diseases and symptoms that were closely related to the disease(s) of interest.

In the causes-diseases-only matrix, there were 8046 causes (MeSH terminology) and 4147 diseases (MeSH Headings No Explode). Causes that could be viewed as quasi-universal were those that impacted more than a threshold number of diseases.

For identifying indirect foundational causes, two matrices were plotted with this data sharing a common axis. The upper matrix was a square symmetrical matrix of diseases and symptoms (hereafter abbreviated as Diseases) on each axis. The lower matrix was a plot of causes vs Diseases. The intersection of cause i with Disease j was defined as a direct cause of Disease j if the matrix cell contained an entry(s), and a possible indirect cause if the matrix cell did not contain an entry.

To identify potential indirect causes of Disease j, direct causes of Diseases strongly associated with Disease j were identified, and hypothesized to be indirect causes of Disease j. Thus, for example, if Hypertension is shown to be strongly related to CKD, and substance X was a direct cause of Hypertension but not a direct cause of CKD, then substance X is hypothesized to be an indirect cause of CKD. The stronger the relationship between the two Diseases, and the more strong pathways that exist linking other Diseases (for which substance X is a direct cause) to CKD, the stronger will be the basis for the assumption that substance X is a potential indirect cause of CKD, and is in fact a Discovery in the Swanson sense of discovery (heretofore applied only to potential treatments).

What constitutes a strong relationship/association between two Diseases that would form a credible basis for hypothesizing potential discovery of indirect causes? Two metrics were examined. One metric was co-occurrence of two Disease MeSH terms well beyond that expected randomly. Thus, if there are Nt total records in a database, the probability of MeSH term A occuring in any one record would be Na (the number of records that contain MeSH term A in the database) divided by Nt, the probability of MeSH term B occurring in any one record would be Nb/Nt, the probability of MeSH terms A and B co-occurring in one record by chance would be Na/Nt*Nb/Nt, and the co-occurrence expected by chance would be Na/Nt*Nb/Nt*Nt, or (Na*Nb)/Nt. Thus, if the actual co-occurrence Cab of two Disease MeSH terms A and B is substantially larger than (Na*Nb)/Nt, the linkage between Diseases A and B is assumed to be strong. The higher the ratio of actual co-occurrence to expected co-occurrence, the stronger is the assumed relationship.

The other metric examined was the Inclusion Index based on the smaller of the two frequencies of occurrence, defined as Cab/Min(Na,Nb). Because of behavior at the limits, the latter metric was selected. The Disease-Disease matrix was normalized using the Inclusion Index. The combination of the causes-Diseases matrix and the normalized Diseases-Diseases matrix formed a causes-Diseases ***network***, which allowed both direct causes to be identified from the causes-Diseases matrix and indirect causes to be identified by tracking potential causes through myriad pathways in the Diseases-Diseases component of the network.

1B1a2. Chemical Registry Number Causes

Pubmed contains two fields called Registry Number and Substance Name. Registry Number contains identifiers representing the substances mentioned in the article when such identifiers are included in the MeSH record for the substance. Substance Name may contain any of 3 types of supplementary concept record (SCR) data: 1) MeSH SCR chemical and drug terms (Class 1); 2) protocol terms (Class 2); and 3) non-MeSH rare disease terms (Class 3) from the NIH Office of Rare Diseases. The MeSH Database and MeSH Browser contain all of these terms.

These two fields are combined into one field in the VP software (Chemical Registry Number), and may contain causes that are not shown in the Title or MeSH Heading. This field was examined for potential causes only in the MeSH Qualifiers-retrieved database. There were no associated linking terms that would allow extraction of causes only, so the CRN terms had to be inspected manually. These terms could be causes, treatments, and biomarkers mainly. They were read to a cutoff frequency, and additional terms were identified at lower frequencies from intersection with lists of toxic materials. All 1,394 resulting CRN causes terms were validated by visual inspection.

1B1b. Generic MeSH Headings Approach

Generic MeSH Headings unambiguously related to causes were identified two ways. Results from past studies were examined, especially the CKD study [12], and generic relevant MeSH Headings were extracted. Second, a few of the most unambiguous generic MeSH terms identified from past studies were entered into Pubmed as query terms, and all the MeSH terms in the resultant retrieval (i.e., those that co-occurred with the entry terms) were examined for relevance. There were 145 terms judged to produce highly relevant results (shown later). These 145 terms constituted the query. Pubmed was also used as the source search engine for the Medline database, for the reasons presented above.

This query was entered into Pubmed for the time interval 1994-2014, 693,450 records (most with Abstracts) were retrieved and downloaded on 18 October 2014, and were imported into the Vantage Point software. 690,486 unique Abstracts were displayed by the software. There were 516,519 MeSH terms (with Qualifiers) listed. All MeSH terms that included at least one of the four Qualifiers shown in the previous MeSH Qualifiers section were placed in a separate group, containing a total of 52,949 MeSH terms with Qualifiers. The software integrated over the MeSH Qualifiers to yield 6,543 MeSH Headings (no Qualifiers shown). These 6,543 MeSH Headings, combined with the 9,038 MeSH Heading causes from the MeSH Qualifiers study in the previous MeSH Qualifiers section, with the 1,394 Chemical Registry Substances extracted in the MeSH Qualifiers study, and with the 13,762 raw text causes extracted from the results of the Title text retrieval study of the next section, were intersected with the 24,231 Top Level MeSH Headings, to yield a total of 8,982 causes. These were the foundational causes for all diseases expressed in MeSH terminology from the relatively unambiguous MeSH Headings retrieval.

1B1c. Title Linking Phrases Approach

Because of limitations from use of MeSH terms (not all records have MeSH descriptors, not all MeSH terms are included in those records that have MeSH, not all MeSH descriptors used have appropriate Qualifiers attached. etc), a text-based approach for identifying causes was added. While the Abstract field would have been most informative and appropriate, computer storage and software limitations would not allow the parsed Abstract field phrases to be opened. Therefore, the record Title field was selected for analysis. A query consisting of two components was used to retrieve the records. The first component consisted of terms that, when they appeared in the Title, were associated with causes in the Title relatively unambiguously. These terms were validated a priori. The second component consisted of terms that, when they co-occurred in the Title with disease names, were associated with causes in the Title relatively unambiguously. The full query used to retrieve records is shown later. This query was entered into Pubmed for the time interval 1989-2014, 616,300 records (many with Abstracts) were retrieved and downloaded on 28 September 2014, and were imported into the Vantage Point software. 536,833 unique Abstracts were displayed by the software. There were 5,452,563 Title phrases listed, which consisted of all single-word, double-word, triple-word, and quadruple-word phrases that did not start or end with stop-words.

The causes in the retrieved records were identified three ways. The parsed Title phrases were examined visually until a threshold frequency, and causes terms were extracted and validated. Given the extremely large number of Title phrases, only a very small fraction could be examined visually. For lower frequency phrases, the strongest linking terms were used to extract potential causes phrases (e.g.,

-induced, -related, -associated, -exposed, caused by, induced by, exposure to, exposed to, etc). The extracted terms were stripped of the linking phrases, combined to avoid duplication, and added to the causes identified visually in the first part. Finally, causes from all other sources, including from past studies, government-approved lists of toxic substances, MeSH-derived causes, and CRN-derived causes, were intersected with the full list of Title phrases, and added to the causes identified in the first two parts.

There were 13,762 validated causes that resulted from from the above extraction techniques. However, many were similar concepts, and could be combined. After a three-step combination approach, 6,480 causes resulted. Some were generic, but most were specific.

1C. Queries used to Retrieve Causes-Related Articles

1C1. MeSH Qualifier Query

MeSH Headings have a number of Qualifiers associated with them to allow focus on items of interest. Thus, the MeSH term Cadmium/toxicity allows records to be retrieved related to the toxicity of Cadmium. These Qualifiers may be perceived as linking terms to the MeSH Headings, allowing for 'surgical' extraction of MeSH Headings that meed desired criteria. Thus, if Qualifiers strongly related to causes can be identified, they can be used to identify MeSH Headings that are potential causes of disease. As shown previously, the four MeSH Qualifiers listed below were selected as the query.

Query

adverse effects [sh] OR toxicity [sh] OR pathogenicity [sh] OR poisoning [sh]

1C2. Title Text Term Query

Because many Medline records do not contain MeSH terms, and because MeSH term assignment may not always be complete, it was decided to augment the MeSH queries with a text query. This query consists of two parts: standalone terms, and terms that are intersected with diseases. Most were derived by examining Titles of records that addressed causes of disease, and selecting those terms that tended to appear frequently with the causes. The diseases used for the second group of terms were obtained by starting with Pubmed's list of all diseases (in MeSH terminology), converting them to text form, consolidating diseases to more generic descriptors, and adding some generic terms not in MeSH (such as cancer*).

1C2a. Standalone Terms

([ti] is the Pubmed tag for Title field)

cardiotoxic* [ti] OR genotoxic* [ti] OR hepatotoxic* [ti] OR immunotoxic* [ti] OR intoxicat* [ti] OR nephrotoxic* [ti] OR neurotoxic* [ti] OR ototoxic* [ti] OR phototoxic* [ti] OR phytotoxic* [ti] OR toxic-effect* [ti] OR toxic-potential* [ti] OR toxic-hazard* [ti] OR toxic-combin* [ti] OR toxicities [ti] OR toxicity

[ti] OR toxicological-effect* [ti] OR toxicological-evaluation* [ti] OR toxicological-impact* [ti] OR toxicological-hazard* [ti] OR toxicological-assessment* [ti] OR toxin-associated [ti] OR toxin-related [ti] OR toxin-injur* [ti] OR toxin-risk* [ti] OR lethal-toxin* [ti] OR (toxin* [ti] AND (fatal* [ti] OR adverse [ti] OR morbid* [ti] OR mortality [ti] or anaphyla* [ti] OR harm [ti] OR damag* [ti] OR deteriorat* [ti] OR exacerbat* [ti] OR trigger* [ti] OR aggravat* [ti])) OR injury-associated [ti] OR risk-associated [ti] OR virus-associated [ti] OR (Ionizing [ti] AND risk* [ti]) OR (risk-of [ti] AND adverse [ti]) OR (adverse-health-effect* [ti] AND (effects-of [ti] OR effect-of [ti])) OR adverse-effect* [ti] OR injury-following [ti] OR related-consequences [ti] OR therapy-related [ti] OR traffic-related [ti] OR health-consequences [ti] OR long-term consequences [ti] OR anaphylactic-reaction* [ti] OR cutaneous-reaction* [ti] OR hypersensitivity-reaction* [ti] OR transfusion-reaction* [ti] OR skin-reaction* [ti] OR inflammation-reaction* [ti] OR inflammatory-reaction* [ti] OR reaction-associated [ti] OR foreign-body-reaction* [ti] OR tissue-reaction* [ti] OR infusion-reaction* [ti] OR systemic-reaction* [ti] OR (allergic [ti] AND reaction-to [ti]) OR teratogenicity [ti] OR teratogenic-effect* [ti] OR advanced-glycation [ti] OR allergenicity [ti] OR bioaccumulation [ti] OR carcinogen [ti] OR Carcinogenic [ti] OR carcinogenicity [ti] OR contaminat* [ti] OR disrupting-chemical* [ti] OR ((effects [ti] OR effect [ti]) AND subchronic [ti]) OR ((effects-of [ti] OR effect-of [ti]) AND prenatal [ti]) OR envenomation [ti] OR fatalities [ti] OR high-fat [ti] OR mutagenicity [ti] OR poisons [ti] OR poisoning [ti] OR precipitated-by [ti] OR precipitated-after [ti] OR precipitated-following [ti] OR side-effect* [ti] OR teratogenesis [ti] OR deleterious-effect* [ti] OR detrimental-effect* [ti] OR late-effect* [ti] OR adverse-metabolic-effect* [ti] OR adverse-renal-effect* [ti] OR respiratory-effect* [ti] OR negative-effect* [ti] OR adverse-reaction* [ti] OR (adversity [ti] AND (early [ti] OR child* [ti] OR life* [ti] OR social [ti] OR family [ti])) OR causative-agent [ti] OR caused-by [ti] OR exposure-to [ti] OR exposed-to [ti] OR exposures [ti] OR (damage-in [ti] AND mice [ti]) OR (damage-in [ti] AND rats [ti]) OR hepatic-damage [ti] OR liver-damage [ti] OR ((increased-risk* [ti] OR complications [ti] OR mutagenic [ti] OR adverse-outcome* [ti] OR life-threatening [ti] OR lung-injury [ti] OR renal-injury [ti] OR susceptibility [ti] OR adverse [ti] OR allergic-reaction* [ti] OR anaphyla* [ti] OR cognitive-dysfunction [ti] OR cardiac-dysfunction [ti] OR (dysfunction [ti] AND in-rats [ti]) OR erectile-dysfunction [ti] OR renal-dysfunction [ti] OR mitochondrial-dysfunction [ti] OR endothelial-dysfunction [ti] OR sexual-dysfunction [ti] OR ventricular-dysfunction [ti] OR allograft-dysfunction [ti] OR thyroid-dysfunction [ti] OR graft-dysfunction [ti] OR liver-dysfunction [ti] OR diastolic-dysfunction [ti] OR vascular-dysfunction [ti] OR organ-dysfunction [ti] OR barrier-dysfunction [ti] OR myocardial-dysfunction [ti] OR systolic-dysfunction [ti] OR voiding-dysfunction [ti] OR hepatic-dysfunction [ti] OR bladder-dysfunction [ti] OR bowel-dysfunction [ti] OR urinary-dysfunction [ti] OR swallowing-dysfunction [ti] OR anorectal-dysfunction [ti] OR cardiopulmonary-dysfunction [ti] OR fatal [ti] OR fibrosis [ti] OR high-incidence [ti] OR iatrogenic [ti] OR mortality [ti] OR morbidity [ti] OR risk* [ti]) AND (after [ti] OR following [ti] OR related-to [ti] OR resulting-from [ti] OR due-to [ti]))

1C2b. Intersect with Diseases

(Expos* [ti] OR induce [ti] OR induced [ti] OR induces [ti] OR incarceration [ti] OR occupation* [ti] OR pathogen* [ti] OR pollut* [ti] OR poverty [ti] OR socioeconomic [ti] OR worker*) AND (Abdominal-Pregnancy [ti] OR Aberrant-Crypt-Foci [ti] OR Abnormal-Karyotype [ti] OR Abnormal-Reflex [ti] OR Abnormalities [ti] OR Abnormality [ti] OR Abortion [ti] OR Abruptio-Placentae [ti] OR Abscess* [ti] OR Acalculous-Cholecystitis [ti] OR Acanthamoeba-Keratitis [ti] OR Acantholysis [ti] OR Acanthosis-Nigricans

[ti] OR Acatalasia [ti] OR Accelerated-Idioventricular-Rhythm [ti] OR Accessory-Atrioventricular-Bundle [ti] OR Achlorhydria [ti] OR Achondroplasia [ti] OR Acid-Base-Imbalance* [ti] OR Acidosis [ti] OR Acne-Keloid [ti] OR Acne-Vulgaris [ti] OR Acrocephalosyndactylia [ti] OR Acrodermatitis [ti] OR Acrodynia [ti] OR Acromegaly [ti] OR Acro-Osteolysis [ti] OR Acrospiroma [ti] OR Actinomycosis [ti] OR Activated-Protein-C-Resistance [ti] OR Acute-Abdomen [ti] OR Acute-Generalized-Exanthematous-Pustulosis [ti] OR Acute-Kidney-Injury [ti] OR Acute-Lung-Injury [ti] OR Acute-Phase-Reaction [ti] OR Adenocarcinoma* [ti] OR Adenofibroma [ti] OR Adenolymphoma [ti] OR Adenoma* [ti] OR Adenomyoma [ti] OR Adenomyosis [ti] OR Adenosarcoma [ti] OR Adiposis-Dolorosa [ti] OR Adrenal-Insufficiency [ti] OR Adrenocortical-Hyperfunction [ti] OR Adrenoleukodystrophy [ti] OR Aerophagy [ti] OR Afibrinogenemia [ti] OR African-Horse-Sickness [ti] OR Agammaglobulinemia [ti] OR Agenesis-of-Corpus-Callosum [ti] OR Ageusia [ti] OR Aggressive-Periodontitis [ti] OR Agnosia [ti] OR Agranulocytosis [ti] OR Agraphia [ti] OR AIDS-Arteritis [ti] OR AIDS-Dementia-Complex [ti] OR AIDS-Related-Complex [ti] OR Airway-Obstruction* [ti] OR Airway-Remodeling [ti] OR Akathisia [ti] OR Akinetic-Mutism [ti] OR Albinism [ti] OR Albuminuria [ti] OR Alcohol-Withdrawal-Delirium [ti] OR Alcohol-Withdrawal-Seizures [ti] OR Alcoholism [ti] OR Alexia [ti] OR Alkalosis [ti] OR Alkaptonuria [ti] OR Alopecia [ti] OR alpha-1-Antitrypsin-Deficiency [ti] OR alpha-Mannosidosis [ti] OR alpha-Thalassemia [ti] OR Alternariosis [ti] OR Altitude-Sickness [ti] OR Alveolar-Bone-Loss [ti] OR Alveolitis [ti] OR Amaurosis-Fugax [ti] OR Amblyopia [ti] OR Amebiasis [ti] OR Ameloblastoma [ti] OR Amelogenesis-Imperfecta [ti] OR Amenorrhea [ti] OR Amino-Acid-Metabolism [ti] OR Amnesia [ti] OR amyloid-Plaque [ti] OR Amyloidosis [ti] OR Anaemia [ti] OR Anaphylaxis [ti] OR Anaplasia [ti] OR Anaplasmosis [ti] OR Anastomotic-Leak [ti] OR Ancylostomiasis [ti] OR Anemia [ti] OR Anencephaly [ti] OR Anetoderma [ti] OR Aneurysm [ti] OR Angina [ti] OR Angiodysplasia [ti] OR Angioedema* [ti] OR Angiofibroma [ti] OR Angioid-Streaks [ti] OR Angiokeratoma [ti] OR Angiolipoma [ti] OR Angiomatosis [ti] OR Angiomyolipoma [ti] OR Anhedonia [ti] OR Aniridia [ti] OR Anisakiasis [ti] OR Aniseikonia [ti] OR Anisocoria [ti] OR Anisometropia [ti] OR Ankylosis [ti] OR Anodontia [ti] OR Anomia [ti] OR Anophthalmos [ti] OR Anorexia [ti] OR Anovulation [ti] OR Anoxia [ti] OR Anthracosilicosis [ti] OR Anthracosis [ti] OR Anthrax [ti] OR Antithrombin-III-Deficiency [ti] OR Anuria [ti] OR Aortic-Coarctation [ti] OR Aortic-Valve-Insufficiency [ti] OR Aortic-Valve-Prolapse [ti] OR Aortitis [ti] OR Aphakia [ti] OR Aphasia [ti] OR Aphonia [ti] OR Aplasia [ti] OR Apnea [ti] OR Apoptosis [ti] OR Appendicitis [ti] OR Apraxia [ti] OR Apraxias [ti] OR Arachnoid-Cyst* [ti] OR Arachnoiditis [ti] OR Arcus-Senilis [ti] OR Argininosuccinic-Aciduria [ti] OR Argyria [ti] OR Arnold-Chiari-Malformation [ti] OR Arrhythmia* [ti] OR Arterial-Stiffness [ti] OR Arterio-Arterial-Fistula [ti] OR Arteriolosclerosis [ti] OR Arteriosclerosis [ti] OR Arteriovenous-Fistula [ti] OR Arteriovenous-Malformations [ti] OR Arteritis [ti] OR Arthralgia [ti] OR Arthritis [ti] OR Arthrogryposis [ti] OR Arthropathy [ti] OR Arthus-Reaction [ti] OR Artificial-Lens-Implant-Migration [ti] OR Asbestosis [ti] OR Ascariasis [ti] OR Ascaridiasis [ti] OR Ascites [ti] OR Ascorbic-Acid-Deficiency [ti] OR Aspergillosis [ti] OR Asphyxia [ti] OR Asthenia [ti] OR Asthenopia [ti] OR Asthenozoospermia [ti] OR Asthma [ti] OR Astigmatism [ti] OR Astrocytoma [ti] OR Ataxia [ti] OR Atherosclerosis [ti] OR atherosclerotic-plaque [ti] OR Athetosis [ti] OR Atrial-Fibrillation [ti] OR Atrial-Flutter [ti] OR Atrial-Premature-Complexes [ti] OR Atrial-Remodeling [ti] OR Atrioventricular-Block [ti] OR Atrophic-Vaginitis [ti] OR Atrophy [ti] OR Autolysis [ti] OR Autonomic-Dysreflexia [ti] OR Avian-Leukosis [ti] OR Avitaminosis [ti] OR Azoospermia [ti] OR Azotemia [ti] OR Babesiosis [ti] OR babinski-Reflex [ti] OR Bacteremia [ti] OR Bacteriuria [ti] OR Balanitis [ti] OR Balanitis-Xerotica-Obliterans [ti] OR Balantidiasis [ti] OR Barrett-Esophagus [ti] OR Bell-Palsy [ti] OR Bell's-Palsy [ti] OR Beriberi [ti] OR Berylliosis [ti] OR beta-Thalassemia [ti] OR Bile-Reflux [ti] OR Biliary-Atresia [ti] OR Biliary-Dyskinesia [ti]

OR Biliary-Fistula [ti] OR Binge-Drinking [ti] OR Biotinidase-Deficiency [ti] OR Bird-Fancier's-Lung [ti] OR Birth-Injuries [ti] OR Birth-Weight [ti] OR Bladder-Exstrophy [ti] OR Blast-Crisis [ti] OR Blastomycosis [ti] OR Blepharitis [ti] OR Blepharoptosis [ti] OR Blepharospasm [ti] OR Blindness [ti] OR Blister* [ti] OR Blood-Group-Incompatibility [ti] OR Blood-Loss [ti] OR Bluetongue [ti] OR Body-Weight [ti] OR Bone-Anteversion [ti] OR Bone-Cysts [ti] OR Bone-Demineralization [ti] OR Bone-Malalignment [ti] OR Bone-Resorption [ti] OR Bone-Retroversion [ti] OR Botulism [ti] OR Brachial-Plexus-Neuritis [ti] OR Brachydactyly [ti] OR Bradycardia [ti] OR Brain-Concussion [ti] OR Brain-Damage [ti] OR Brain-Death [ti] OR Brain-Injur* [ti] OR Brain-Ischemia [ti] OR Branchioma [ti] OR Breast-Cyst* [ti] OR Breech-Presentation [ti] OR Brenner-Tumor* [ti] OR Bronchial-Fistula [ti] OR Bronchial-Hyperreactivity [ti] OR Bronchial-Spasm [ti] OR Bronchiectasis [ti] OR Bronchiolitis [ti] OR Bronchitis [ti] OR Bronchogenic-Cyst* [ti] OR Bronchomalacia [ti] OR Bronchopneumonia [ti] OR Bronchopulmonary-Sequestration [ti] OR Brucellosis [ti] OR Bruxism [ti] OR Bulbar-Palsy [ti] OR Bulbo-Spinal-Atrophy [ti] OR Bulimia [ti] OR Bundle-Branch-Block [ti] OR Burkitt-Lymphoma [ti] OR Bursitis [ti] OR Buschke-Lowenstein-Tumor* [ti] OR Byssinosis [ti] OR Cachexia [ti] OR CADASIL [ti] OR Cafe-au-Lait-Spots [ti] OR Calcification [ti] OR Calcinosis [ti] OR Calciphylaxis [ti] OR Calculi [ti] OR Callosities [ti] OR Cancer* [ti] OR Candidemia [ti] OR Candidiasis [ti] OR Capsule-Opacification [ti] OR Carbohydrate-Metabolism [ti] OR Carbonyl-Stress [ti] OR Carboxymethyllysine [ti] OR Carcinogenesis [ti] OR Carcinoid-Tumor* [ti] OR Carcinoma* [ti] OR Carcinosarcoma* [ti] OR Cardiac-Arrest [ti] OR Cardiac-Complexes [ti] OR Cardiac-Output [ti] OR Cardiac-Tamponade [ti] OR Cardiogenic-Shock [ti] OR Cardiomegaly [ti] OR Cardiomyopath* [ti] OR cardiovascular-health [ti] OR cardiovascular-outcome* [ti] OR cardiovascular-risk [ti] OR Carney-Complex [ti] OR Carotid-Artery-Dissection [ti] OR Carotid-Artery-Injuries [ti] OR Carotid-Body-Tumor* [ti] OR Carotid-Cavernous-Sinus-Fistula [ti] OR Catalepsy [ti] OR Cataplexy [ti] OR Cataract* [ti] OR Catatonia [ti] OR Causalgia [ti] OR Cellulitis [ti] OR Central-Nervous-System-Cyst* [ti] OR Central-Nervous-System-Helminthiasis [ti] OR Central-Nervous-System-Vascular-Malformation* [ti] OR Central-Serous-Chorioretinopathy [ti] OR Cephalopelvic-Disproportion [ti] OR Cerebellar-Ataxia [ti] OR Cerebral-Amyloid-Angiopathy [ti] OR Cerebral-Palsy [ti] OR Cerebral-Phaeohyphomycosis [ti] OR Cerebral-Ventriculitis [ti] OR Cerebrospinal-Fluid-Otorrhea [ti] OR Cerebrospinal-Fluid-Rhinorrhea [ti] OR Cerebrovascular-Trauma [ti] OR Cervical-Intraepithelial-Neoplasia [ti] OR Chagas-Cardiomyopathy [ti] OR Chalazion [ti] OR Chancre [ti] OR Chancroid [ti] OR Channelopathies [ti] OR Cheilitis [ti] OR Cheyne-Stokes-Respiration [ti] OR Chickenpox [ti] OR Chills [ti] OR Chloracne [ti] OR Choanal-Atresia [ti] OR Cholangiocarcinoma [ti] OR Cholangitis [ti] OR Cholecystitis [ti] OR Cholecystolithiasis [ti] OR Choledochal-Cyst* [ti] OR Choledocholithiasis [ti] OR Cholelithiasis [ti] OR Cholera [ti] OR Cholestasis [ti] OR Cholesteatoma [ti] OR Choline-Deficiency [ti] OR Chondroblastoma [ti] OR Chondrocalcinosis [ti] OR Chondrodysplasia-Punctata [ti] OR Chondroma [ti] OR Chondromalacia-Patellae [ti] OR Chondrosarcoma [ti] OR Chordoma [ti] OR Chorea [ti] OR Chorioamnionitis [ti] OR Choriocarcinoma [ti] OR Chorioretinitis [ti] OR Choristoma [ti] OR Choroidal-Neovascularization [ti] OR Choroiditis [ti] OR Chromoblastomycosis [ti] OR Chromosomal-Instability [ti] OR Chromosome-Aberration* [ti] OR Chromosome-Breakage [ti] OR Chromosome-Fragility [ti] OR Chromosome-Inversion [ti] OR Chylothorax [ti] OR Chylous-Ascites [ti] OR Cicatrix [ti] OR Citrullinemia [ti] OR Cleft-Lip [ti] OR Cleft-Palate [ti] OR Clonorchiasis [ti] OR Clubfoot [ti] OR Cluster-Headache* [ti] OR Coccidioidomycosis [ti] OR Coccidiosis [ti] OR Colic [ti] OR Colitis [ti] OR Collagenous-Sprue [ti] OR Colloid-Cysts [ti] OR Coloboma [ti] OR Colonic-Polyps [ti] OR Colonic-Pseudo-Obstruction [ti] OR Color-Vision-Defects [ti] OR Coma [ti] OR Common-Cold [ti] OR Common-Variable-Immunodeficiency [ti] OR Commotio-Cordis [ti] OR Complication* [ti] OR Condylomata-Acuminata [ti]

OR Confusion [ti] OR Congenital-Hyperinsulinism [ti] OR Congenital-Hypothyroidism [ti] OR Conjoined-Twins [ti] OR Conjunctivitis [ti] OR Constipation [ti] OR Constriction [ti] OR Contracture [ti] OR Coproporphyria [ti] OR Cor-Triatriatum [ti] OR Corneal-Dystrophies [ti] OR Corneal-Endothelial-Cell-Loss [ti] OR Corneal-Neovascularization [ti] OR Corneal-Opacity [ti] OR Corneal-Perforation [ti] OR Corneal-Wavefront-Aberration [ti] OR Coronary-Aneurysm* [ti] OR Coronary-Occlusion [ti] OR Coronary-Vasospasm* [ti] OR Coronary-Vessel-Anomalies [ti] OR Cough [ti] OR Cowpox [ti] OR Coxa-Valga [ti] OR Coxa-Vara [ti] OR Craniocerebral-Trauma [ti] OR Craniofacial-Dysostosis [ti] OR Craniopharyngioma [ti] OR Craniosynostoses [ti] OR Croup [ti] OR Cryoglobulinemia [ti] OR Cryptococcosis [ti] OR Cryptogenic-Organizing-Pneumonia [ti] OR Cryptorchidism [ti] OR Cryptosporidiosis [ti] OR Cutaneous-Fistula [ti] OR Cutis-Laxa [ti] OR Cyanosis [ti] OR Cyclosporiasis [ti] OR Cystadenocarcinoma [ti] OR Cystadenoma [ti] OR Cystic-Fibrosis [ti] OR Cysticercosis [ti] OR Cystinosis [ti] OR Cystinuria [ti] OR Cystitis [ti] OR Cystocele [ti] OR Cysts [ti] OR Cytochrome-c-Oxidase-Deficiency [ti] OR Cytomegalovirus-Retinitis [ti] OR Dacryocystitis [ti] OR Dandruff [ti] OR Deafness [ti] OR Decalcification [ti] OR Decerebrate-State [ti] OR Dehydration [ti] OR Delayed-Emergence-from-Anesthesia [ti] OR Delayed-Graft-Function [ti] OR Delayed-Puberty [ti] OR Delirium [ti] OR Delta-Thalassemia [ti] OR Dementia [ti] OR Dendritic-Cell-Sarcoma [ti] OR Dengue [ti] OR Dental-Calculus [ti] OR Dental-Caries [ti] OR Dental-Deposits [ti] OR Dental-Enamel-Hypoplasia [ti] OR Dental-Fissures [ti] OR Dental-Fistula [ti] OR Dental-Leakage [ti] OR Dental-Occlusion [ti] OR Dental-Plaque [ti] OR Dental-Pulp-Calcification [ti] OR Dental-Pulp-Exposure [ti] OR Dental-Pulp-Necrosis [ti] OR Dentigerous-Cyst [ti] OR Dentin-Sensitivity [ti] OR Dentinogenesis-Imperfecta [ti] OR Dentofacial-Deformities [ti] OR Depression [ti] OR Dermatitis [ti] OR Dermatofibrosarcoma [ti] OR Dermatomycoses [ti] OR Dermatomyositis [ti] OR Dermoid-Cyst [ti] OR Desmoplastic-Small-Round-Cell-Tumor* [ti] OR Dextrocardia [ti] OR Diabetes [ti] OR Diabetic [ti] OR Diaper-Rash [ti] OR Diaphragmatic-Eventration [ti] OR Diarrhea [ti] OR Diastema [ti] OR Dicrocoeliasis [ti] OR Dientamoebiasis [ti] OR Diffuse-Axonal-Injury [ti] OR Digestive-System-Fistula [ti] OR Dihydropyrimidine-Dehydrogenase-Deficiency [ti] OR Dilatation [ti] OR Diphtheria [ti] OR Diphyllobothriasis [ti] OR Diplopia [ti] OR Dirofilariasis [ti] OR Discitis [ti] OR Disease* [ti] OR [ti] OR Disorder* [ti] OR Disseminated-Intravascular-Coagulation [ti] OR Distemper [ti] OR Diurnal-Enuresis [ti] OR Diverticulitis [ti] OR Diverticulosis [ti] OR Diverticulum [ti] OR Dizziness [ti] OR Double-Outlet-Right-Ventricle [ti] OR Dracunculiasis [ti] OR Drowning [ti] OR Drug-Hypersensitivity [ti] OR Drug-Overdose [ti] OR Drug-Induced-Liver-Injury [ti] OR Dry-Socket [ti] OR Ductus-Arteriosus [ti] OR Duodenal-Obstruction* [ti] OR Duodenitis [ti] OR Duodenogastric-Reflux [ti] OR Dupuytren-Contracture [ti] OR Dwarfism [ti] OR Dysarthria [ti] OR Dysautonomia [ti] OR Dysbiosis [ti] OR Dyscalculia [ti] OR Dysentery [ti] OR Dysfunction* [ti] OR Dysgammaglobulinemia [ti] OR Dysgerminoma [ti] OR Dysgeusia [ti] OR Dyskeratosis-Congenita [ti] OR Dyskinesia* [ti] OR Dyslexia [ti] OR Dyslipid* [ti] OR Dysmenorrhea [ti] OR Dysostoses [ti] OR Dyspareunia [ti] OR Dyspepsia [ti] OR Dysphonia [ti] OR Dysplasia [ti] OR Dyspnea [ti] OR Dyssomnias [ti] OR Dystocia [ti] OR Dystonia [ti] OR Dysuria [ti] OR Ear-Deformities [ti] OR Earache [ti] OR Ebstein-Anomaly [ti] OR Ecchymosis [ti] OR Eccrine-Porocarcinoma [ti] OR Echinococcosis [ti] OR Echinostomiasis [ti] OR Eclampsia [ti] OR Ecthyma [ti] OR Ectoparasitic-Infestations [ti] OR Ectopia-Cordis [ti] OR Ectopia-Lentis [ti] OR ectopic-Pregnancy [ti] OR Ectromelia [ti] OR Ectropion [ti] OR Eczema [ti] OR Edema* [ti] OR edentulous-Mouth [ti] OR Egg-Hypersensitivity [ti] OR Ehrlichiosis [ti] OR Eisenmenger-Complex [ti] OR Elephantiasis [ti] OR Elliptocytosis [ti] OR Emaciation [ti] OR Embolism* [ti] OR Embryo-Loss [ti] OR Emergencies [ti] OR Emphysema [ti] OR Emphysematous-Cholecystitis [ti] OR Empyema [ti] OR Encephalitis [ti] OR Encephalitozoonosis [ti] OR Encephalocele [ti] OR Encephalomalacia [ti] OR Encephalomyelitis [ti] OR Encephalopathy [ti] OR Enchondromatosis [ti] OR

Endarteritis [ti] OR Endocardial-Cushion-Defects [ti] OR Endocardial-Fibroelastosis [ti] OR Endocarditis [ti] OR Endodermal-Sinus-Tumor* [ti] OR Endoleak [ti] OR Endolymphatic-Hydrops [ti] OR Endometrial-Stromal-Tumors* [ti] OR Endometriosis [ti] OR Endometritis [ti] OR Endophthalmitis [ti] OR Endotoxemia [ti] OR Enophthalmos [ti] OR Entamoebiasis [ti] OR Enteritis [ti] OR Enterobiasis [ti] OR Enterocolitis [ti] OR Enterotoxemia [ti] OR Entropion [ti] OR Enuresis [ti] OR Enzootic-Bovine-Leukosis [ti] OR Eosinophilia [ti] OR Eosinophilic-Granuloma [ti] OR Ependymoma [ti] OR Epidermal-Cyst* [ti] OR Epidermodysplasia-Verruciformis [ti] OR Epidermolysis-Bullosa [ti] OR Epididymitis [ti] OR Epiglottitis [ti] OR Epilepsia-Partialis-Continua [ti] OR Epilepsies [ti] OR Epilepsy [ti] OR Epiphyses [ti] OR Epiretinal-Membrane [ti] OR Epispadias [ti] OR Epistaxis [ti] OR Equinus-Deformity [ti] OR Erectile-Dysfunction [ti] OR Ergotism [ti] OR Eructation [ti] OR Eruption* [ti] OR Erysipelas [ti] OR Erysipeloid [ti] OR Erythema* [ti] OR Erythroblastosis [ti] OR Erythrokeratodermia-Variabilis [ti] OR Erythromelalgia [ti] OR Erythroplasia [ti] OR Esophageal-Achalasia [ti] OR Esophageal-and-Gastric-Varices [ti] OR Esophageal-Atresia [ti] OR Esophageal-Cyst* [ti] OR Esophageal-Fistula [ti] OR Esophageal-Perforation* [ti] OR Esophageal-Spasm* [ti] OR Esophagitis [ti] OR Esotropia [ti] OR Essential-Tremor* [ti] OR Esthesioneuroblastoma [ti] OR Ethmoid-Sinusitis [ti] OR Exanthema [ti] OR Exocrine-Pancreatic-Insufficiency [ti] OR Exophthalmos [ti] OR Exostoses [ti] OR Exotropia [ti] OR Exsanguination [ti] OR Eye-Injuries [ti] OR Facial-Asymmetry [ti] OR Facial-Dermatoses [ti] OR Facial-Hemiatrophy [ti] OR Facial-Neuralgia [ti] OR Facial-Paralysis [ti] OR Factor-V-Deficiency [ti] OR Factor-VII-Deficiency [ti] OR Factor-X-Deficiency [ti] OR Factor-XI-Deficiency [ti] OR Factor-XII-Deficiency [ti] OR Factor-XIII-Deficiency [ti] OR Failure-to-Thrive [ti] OR Familial-Hypophosphatemic-Rickets [ti] OR Fanconi-Anemia [ti] OR Farmer's-Lung [ti] OR Fasciculation [ti] OR Fasciitis [ti] OR Fascioliasis [ti] OR Fascioloidiasis [ti] OR Fatigue [ti] OR Fatty-Liver [ti] OR Favism [ti] OR Febrile-Neutropenia [ti] OR Fecal-Impaction [ti] OR Fecal-Incontinence [ti] OR Feline-Panleukopenia [ti] OR Feminization [ti] OR Femoracetabular-Impingement [ti] OR Fetal-Death* [ti] OR Fetal-Distress [ti] OR Fetal-Growth-Retardation [ti] OR Fetal-Hypoxia [ti] OR Fetal-Macrosomia [ti] OR Fetal-Membranes [ti] OR Fetal-Resorption [ti] OR Fetal-Weight [ti] OR Fetofetal-Transfusion [ti] OR Fetomaternal-Transfusion [ti] OR Fever [ti] OR Fibroadenoma* [ti] OR Fibroma* [ti] OR Fibromatosis [ti] OR Fibromyalgia [ti] OR Fibrosarcoma [ti] OR Fibrosis [ti] OR Fibrous-Tumor* [ti] OR Filariasis [ti] OR Fissure-in-Ano [ti] OR Fissured-Tongue [ti] OR Fistula [ti] OR Flatfoot [ti] OR Flatulence [ti] OR Flea-Infestation* [ti] OR Fluorosis [ti] OR Flushing [ti] OR Focal-Dermal-Hypoplasia [ti] OR Folic-Acid-Deficiency [ti] OR Follicular-Cyst* [ti] OR Folliculitis [ti] OR Food-Hypersensitivity [ti] OR Foot-Deformities [ti] OR Foot-Dermatoses [ti] OR Foramen-Ovale [ti] OR Foreign-Body-Reaction* [ti] OR Fournier-Gangrene [ti] OR Fowlpox [ti] OR Freemartinism [ti] OR Friedreich-Ataxia [ti] OR Frontal-Sinusitis [ti] OR Frontotemporal-Dementia [ti] OR Frontotemporal-Lobar-Degeneration [ti] OR Fructose-Intolerance [ti] OR Fructose-1,6-Diphosphatase-Deficiency [ti] OR Fuchs'-Endothelial-Dystrophy [ti] OR Fucosidosis [ti] OR Fungemia [ti] OR Funnel-Chest [ti] OR Furcation-Defects [ti] OR Furunculosis [ti] OR Fusariosis)

(Expos* [ti] OR induce [ti] OR induced [ti] OR induces [ti] OR incarceration [ti] OR occupation* [ti] OR pathogen* [ti] OR pollut* [ti] OR poverty [ti] OR socioeconomic [ti] OR worker*) AND (Gagging [ti] OR Gait-Apraxia [ti] OR Gait-Ataxia [ti] OR Galactorrhea [ti] OR Galactosemia* [ti] OR Gallstone* [ti] OR Ganglioglioma [ti] OR Ganglion-Cyst* [ti] OR Ganglioneuroblastoma [ti] OR Ganglioneuroma* [ti] OR Gangliosidosis [ti] OR Gangrene [ti] OR Gastric-Antral-Vascular-Ectasia [ti] OR Gastric-Dilatation [ti] OR Gastric-Fistula [ti] OR Gastric-Outlet-Obstruction* [ti] OR Gastrinoma [ti] OR Gastritis [ti] OR

Gastroenteritis [ti] OR Gastroesophageal-Reflux [ti] OR Gastrointestinal-Stromal-Tumor* [ti] OR Gastroparesis [ti] OR Gastroschisis [ti] OR Genomic-Instability [ti] OR Genu-Valgum [ti] OR Genu-Varum [ti] OR Geographic-Atrophy [ti] OR Geotrichosis [ti] OR Germinoma [ti] OR Giant-Cell-Arteritis [ti] OR Giant-Cell-Tumor-of-Bone [ti] OR Giant-Cell-Tumor* [ti] OR Giardiasis [ti] OR Gigantism [ti] OR Gingival-Hypertrophy [ti] OR Gingival-Overgrowth [ti] OR Gingival-Pocket* [ti] OR Gingival-Recession [ti] OR Gingivitis [ti] OR Glanders [ti] OR Glaucoma [ti] OR Glioblastoma [ti] OR Glioma [ti] OR Gliosarcoma [ti] OR Gliosis [ti] OR Glomerulonephritis [ti] OR Glomerulosclerosis [ti] OR Glomus-Jugulare-Tumor* [ti] OR Glomus-Tumor* [ti] OR Glomus-Tympanicum-Tumor* [ti] OR Glossalgia [ti] OR Glossitis [ti] OR Glucagonoma [ti] OR Glucose-Intolerance [ti] OR Glucosephosphate-Dehydrogenase-Deficiency [ti] OR Glycat* [ti] OR Glycemia [ti] OR Glycosuria [ti] OR Glycosylat* [ti] OR Glycoxidation [ti] OR Gnathostomiasis [ti] OR Goiter [ti] OR Gonadal-Dysgenesis [ti] OR Gonorrhea [ti] OR Gout [ti] OR Graft-Occlusion* [ti] OR Granular-Cell-Tumor* [ti] OR Granuloma* [ti] OR Granulomatosis [ti] OR Granulomatous-Mastitis [ti] OR Granulosa-Cell-Tumor* [ti] OR Graves-Ophthalmopathy [ti] OR Gynatresia [ti] OR Gynecomastia [ti] OR Gyrate-Atrophy [ti] OR Haematuria [ti] OR Haemonchiasis [ti] OR Hairy-Tongue [ti] OR Halitosis [ti] OR Hallucination* [ti] OR Hallux-Rigidus [ti] OR Hallux-Valgus [ti] OR Hallux-Varus [ti] OR Hamartoma [ti] OR Hand-Deformities [ti] OR Hand-Dermatoses [ti] OR Haploinsufficiency [ti] OR Hazard* [ti] OR Head-Injur* [ti] OR Headache* [ti] OR Hearing-Loss [ti] OR Heart-Aneurysm* [ti] OR Heart-Arrest [ti] OR Heart-Block* [ti] OR Heart-Defect* [ti] OR Heart-Failure [ti] OR Heart-Murmur* [ti] OR Heart-Septal-Defect* [ti] OR Heartburn [ti] OR Heel-Spur* [ti] OR Helminthiasis [ti] OR Hemangioblastoma [ti] OR Hemangioendothelioma [ti] OR Hemangioma* [ti] OR Hemangiopericytoma [ti] OR Hemangiosarcoma [ti] OR Hemarthrosis [ti] OR Hematemesis [ti] OR Hematocele [ti] OR Hematocolpos [ti] OR Hematoma* [ti] OR Hematometra [ti] OR Hematuria [ti] OR Hemianopsia [ti] OR Hemifacial-Spasm* [ti] OR Hemiplegia [ti] OR Hemobilia [ti] OR Hemochromatosis [ti] OR Hemoglobinopathies [ti] OR Hemoglobinuria [ti] OR Hemolysis [ti] OR Hemoperitoneum [ti] OR Hemophilia [ti] OR Hemopneumothorax [ti] OR Hemoptysis [ti] OR Hemorrhag* [ti] OR Hemorrhoids [ti] OR Hemosiderosis [ti] OR Hemospermia [ti] OR Hemothorax [ti] OR Hepatic-Encephalopathy [ti] OR Hepatic-Insufficiency [ti] OR Hepatitis [ti] OR Hepatoblastoma [ti] OR Hepatolenticular-Degeneration [ti] OR Hepatomegaly [ti] OR Hereditary-Angioedema [ti] OR Hernia* [ti] OR Heroin-Dependence [ti] OR Herpangina [ti] OR Herpes-Genitalis [ti] OR Herpes-Labialis [ti] OR Herpes-Simplex [ti] OR Herpes-Zoster [ti] OR Heterotopic-Pregnancy [ti] OR Hiccup* [ti] OR Hidradenitis [ti] OR Hidrocystoma [ti] OR Hip-Contracture [ti] OR Hip-Dislocation* [ti] OR Hirsutism [ti] OR Histiocytic-Necrotizing-Lymphadenitis [ti] OR Histiocytic-Sarcoma [ti] OR Histiocytoma [ti] OR Histiocytosis [ti] OR Histoplasmosis [ti] OR HIV-Enteropathy [ti] OR HIV-Seropositivity [ti] OR HIV/AIDS [ti] OR Hoarseness [ti] OR Holoprosencephaly [ti] OR Homocystinuria [ti] OR Hot-Flashes [ti] OR Hutchinson's-Melanotic-Freckle [ti] OR Hyalohyphomycosis [ti] OR Hydatidiform-Mole [ti] OR Hydranencephaly [ti] OR Hydroa-Vacciniforme [ti] OR Hydrocephalus [ti] OR Hydronephrosis [ti] OR Hydrophthalmos [ti] OR Hydropneumothorax [ti] OR Hydrops-Fetalis [ti] OR Hydrothorax [ti] OR Hymenolepiasis [ti] OR Hyperacusis [ti] OR Hyperaldosteronism [ti] OR Hyperalgesia [ti] OR Hyperammonemia [ti] OR Hyperamylasemia [ti] OR Hyperandrogenism [ti] OR Hyperargininemia [ti] OR Hyperbilirubinemia [ti] OR Hypercalcemi* [ti] OR Hypercalciuria [ti] OR Hypercapnia [ti] OR Hypercellularity [ti] OR Hypercementosis [ti] OR Hypercholesterol* [ti] OR Hypercoagul* [ti] OR Hyperemesis-Gravidarum [ti] OR Hyperemi* [ti] OR Hyperesthesia [ti] OR Hypergammaglobulinemia [ti] OR Hyperglyc* [ti] OR Hyperhidrosis [ti] OR Hyperhomocystein* [ti] OR Hyperinsulin* [ti] OR Hyperkal* [ti] OR Hyperkeratosis [ti] OR Hyperkinesi*

[ti] OR Hyperleptinemia* [ti] OR Hyperlipid* [ti] OR Hyperlipoproteinemia* [ti] OR Hyperlysinemias [ti] OR Hypermagnesemi* [ti] OR Hypernatremia [ti] OR Hyperopia [ti] OR Hyperostosis [ti] OR Hyperoxaluria [ti] OR Hyperoxia [ti] OR Hyperparathyroid* [ti] OR Hyperphagia [ti] OR Hyperphosphat* [ti] OR Hyperpigmentation [ti] OR Hyperpituitarism [ti] OR Hyperplasia [ti] OR Hyperprolactinemia [ti] OR Hypersecretion [ti] OR Hypersensitivity [ti] OR Hypersomnolence [ti] OR Hypersplenism [ti] OR Hypertelorism [ti] OR Hypertension [ti] OR Hypertensive-Encephalopathy [ti] OR Hypertensive-Retinopathy [ti] OR Hyperthyroidism [ti] OR Hyperthyroxinemia [ti] OR Hypertrichosis [ti] OR Hypertriglycerid* [ti] OR Hypertrophy [ti] OR Hyperuric* [ti] OR Hyperventilation [ti] OR Hypervitaminosis [ti] OR Hypervolemia [ti] OR Hypesthesia [ti] OR Hyphema [ti] OR Hypoalbuminemia [ti] OR Hypoaldosteronism [ti] OR Hypoalphalipoproteinemia* [ti] OR Hypobetalipoproteinemia* [ti] OR Hypocalcemi* [ti] OR Hypocapnia [ti] OR Hypodermyiasis [ti] OR Hypoglyc* [ti] OR Hypogonadism [ti] OR Hypohidrosis [ti] OR Hypokalemi* [ti] OR Hypokinesi* [ti] OR Hypolipid* [ti] OR Hypolipoproteinemias [ti] OR Hypomagnesemi* [ti] OR Hypomethylation [ti] OR Hyponatremi* [ti] OR Hypoparathyroidism [ti] OR Hypoperfusion [ti] OR Hypophosphat* [ti] OR Hypopigmentation [ti] OR Hypopituitarism [ti] OR Hypoplasia [ti] OR Hypoprothrombinemia* [ti] OR Hypospadias [ti] OR Hypotension [ti] OR Hypothermia [ti] OR Hypothyroid* [ti] OR Hypotrichosis [ti] OR Hypoventilation [ti] OR Hypovolemia [ti] OR Hypoxemia [ti] OR Hypoxia [ti] OR Ichthyosis [ti] OR IgA-Deficiency [ti] OR IgG-Deficiency [ti] OR Ileitis [ti] OR Ileus [ti] OR Iliac-Aneurysm [ti] OR Illness [ti] OR Illusions [ti] OR Immersion-Foot [ti] OR Immunoblastic-Lymphadenopathy [ti] OR Impacted-Tooth [ti] OR Imperforate-Anus [ti] OR Impetigo [ti] OR Implant-Capsular-Contracture [ti] OR Impotence [ti] OR Incontinentia-Pigmenti [ti] OR Inert-Gas-Narcosis [ti] OR Infarction* [ti] OR Infect* [ti] OR Infertility [ti] OR Inflammation [ti] OR Inflammatory [ti] OR Influenza [ti] OR Ingrown-Nails [ti] OR Inhalant-Abuse* [ti] OR (Injury-in [ti] AND Mice [ti]) OR (injury-in [ti] AND rats [ti]) OR Insect-Bite* [ti] OR Insect-Sting* [ti] OR Insomnia* [ti] OR Insulin-Coma [ti] OR Insulin-Resistance [ti] OR Insulinoma [ti] OR Intellectual-Disability [ti] OR Intermittent-Claudication [ti] OR Interstitial-Pneumonias [ti] OR Intertrigo [ti] OR Intervertebral-Disc-Degeneration [ti] OR Intervertebral-Disc-Displacement [ti] OR Intestinal-Atresia [ti] OR Intestinal-Fistula* [ti] OR Intestinal-Obstruction* [ti] OR Intestinal-Perforation* [ti] OR Intestinal-Polyposis [ti] OR Intestinal-Polyps [ti] OR Intestinal-Pseudo-Obstruction [ti] OR Intestinal-Volvulus [ti] OR Intracranial-Arteriosclerosis [ti] OR Intracranial-Arteriovenous-Malformations [ti] OR Intracranial-Embolism* [ti] OR Intracranial-Hypotension [ti] OR Intraoperative-Awareness [ti] OR Intraoperative-Complications [ti] OR Intussusception [ti] OR Iridocyclitis [ti] OR Iritis [ti] OR Iron-Overload [ti] OR Ischemia [ti] OR Ischemic-Attack [ti] OR Ischemic-Contracture [ti] OR Isolated-Noncompaction-of-the-Ventricular-Myocardium [ti] OR Isosporiasis [ti] OR Jaundice [ti] OR Jaw-Cyst* [ti] OR Joint-Deformities [ti] OR Joint-Instability [ti] OR Joint-Loose-Bodies [ti] OR Keloid [ti] OR Keratitis [ti] OR Keratoacanthoma [ti] OR Keratoconjunctivitis [ti] OR Keratoconus [ti] OR Keratoderma [ti] OR Keratosis [ti] OR Kernicterus [ti] OR Ketosis [ti] OR Kidney-Calculi [ti] OR Kidney-Failure [ti] OR Klatskin's-Tumor [ti] OR Krukenberg-Tumor [ti] OR Kuru [ti] OR Kwashiorkor [ti] OR Kyphosis [ti] OR Labyrinthitis [ti] OR Lacrimal-Duct-Obstruction* [ti] OR Lactose-Intolerance [ti] OR Larva-Migrans [ti] OR Laryngismus [ti] OR Laryngitis [ti] OR Laryngomalacia [ti] OR Laryngopharyngeal-Reflux [ti] OR Laryngostenosis [ti] OR Latex-Hypersensitivity [ti] OR Lathyrism [ti] OR Leber-Congenital-Amaurosis [ti] OR Lecithin-Acyltransferase-Deficiency [ti] OR Leg-Dermatoses [ti] OR Leg-Length-Inequality [ti] OR Legionellosis [ti] OR Leiomyoma [ti] OR Leiomyomatosis [ti] OR Leiomyosarcoma [ti] OR Leishmania* [ti] OR Lens-Subluxation [ti] OR Lentigo [ti] OR Leprosy [ti] OR Leptospirosis [ti] OR Lethargy [ti] OR Leukemia [ti] OR Leukemic-Infiltration [ti] OR Leukemoid-Reaction

[ti] OR Leukoaraiosis [ti] OR Leukocytosis [ti] OR Leukodystrophy [ti] OR Leukoedema [ti] OR Leukoencephalitis [ti] OR Leukoencephalopath* [ti] OR Leukokeratosis [ti] OR Leukomalacia [ti] OR Leukopenia [ti] OR Leukoplakia [ti] OR Leukorrhea [ti] OR Leukostasis [ti] OR Leydig-Cell-Tumor [ti] OR Lice-Infestation* [ti] OR Lichen-Nitidus [ti] OR Lichen-Planus [ti] OR Lichen-Sclerosus-et-Atrophicus [ti] OR Limb-Deformit* [ti] OR Linear-IgA-Bullous-Dermatosis [ti] OR Lingual-Thyroid [ti] OR Linitis-Plastica [ti] OR Lipid-Metabolism [ti] OR Lipidoses [ti] OR Lipid-Peroxid* [ti] OR Lipodystrophy [ti] OR Lipoma [ti] OR Lipomatosis [ti] OR Lipoperoxidation [ti] OR Liposarcoma [ti] OR Lipoxidation [ti] OR Lissencephalies [ti] OR Lissencephaly [ti] OR Listeriosis [ti] OR Lithiasis [ti] OR Livedo-Reticularis [ti] OR Liver-Cirrhosis [ti] OR Liver-Failure [ti] OR Liver-Injury [ti] OR Loiasis [ti] OR Lordosis [ti] OR Low-Tension-Glaucoma [ti] OR Lower-Extremity-Deformit* [ti] OR Lower-Urinary-Tract-Symptom* [ti] OR Ludwig's-Angina [ti] OR Lung-Injury [ti] OR Lupus-Erythematosus [ti] OR Lupus-Nephritis [ti] OR Lupus-Vulgaris [ti] OR Lyme-Neuroborreliosis [ti] OR Lymphadenitis [ti] OR Lymphangiectasis [ti] OR Lymphangioleiomyomatosis [ti] OR Lymphangioma [ti] OR Lymphangiomyoma [ti] OR Lymphangiosarcoma [ti] OR Lymphangitis [ti] OR Lymphatic-Metastas* [ti] OR Lymphedema [ti] OR Lymphocele [ti] OR Lymphocytic-Choriomeningitis [ti] OR Lymphocytosis [ti] OR Lymphogranuloma-Venereum [ti] OR Lymphohistiocytosis [ti] OR Lymphoma [ti] OR Lymphomatoid-Granulomatosis [ti] OR Lymphomatoid-Papulosis [ti] OR Lymphopenia)

(Expos* [ti] OR induce [ti] OR induced [ti] OR induces [ti] OR incarceration [ti] OR occupation* [ti] OR pathogen* [ti] OR pollut* [ti] OR poverty [ti] OR socioeconomic [ti] OR worker*) AND (Macroalbuminuria [ti] OR Macrocephaly [ti] OR Macroglossia [ti] OR Macular-Degeneration [ti] OR Magnesium-Deficiency [ti] OR Malacoplakia [ti] OR Malaria [ti] OR Malformations-of-Cortical-Development [ti] OR Malformed-Nails [ti] OR Malignant-Catarrh [ti] OR Malignant-Hyperthermia [ti] OR Malnutrition [ti] OR Malocclusion [ti] OR Mandibulofacial-Dysostosis [ti] OR Mansonelliasis [ti] OR Marijuana-Abuse [ti] OR Mast-Cell-Sarcoma [ti] OR Mastitis [ti] OR Mastocytoma [ti] OR Mastocytosis [ti] OR Mastodynia [ti] OR Mastoiditis [ti] OR Maternal-Death [ti] OR Maxillary-Sinusitis [ti] OR Measles [ti] OR Meckel-Diverticulum [ti] OR Mediastinal-Cyst [ti] OR Mediastinal-Emphysema [ti] OR Mediastinitis [ti] OR Medullary-Sponge-Kidney [ti] OR Medulloblastoma [ti] OR Megacolon [ti] OR Melanoma* [ti] OR Melanosis [ti] OR Melena [ti] OR Melioidosis [ti] OR Meningeal-Carcinomatosis [ti] OR Meningioma* [ti] OR Meningism [ti] OR Meningitis [ti] OR Meningocele [ti] OR Meningoencephalitis [ti] OR Meningomyelocele [ti] OR Menopause [ti] OR Menorrhagia [ti] OR Menstruation-Disturbances [ti] OR Mental-Fatigue [ti] OR Mental-Retardation [ti] OR Mesenchymoma [ti] OR Mesenteric-Cyst* [ti] OR Mesenteric-Lymphadenitis [ti] OR Mesenteric-Vascular-Occlusion [ti] OR Mesial-Movement-of-Teeth [ti] OR Mesothelioma [ti] OR Metabolic-Acidosis [ti] OR Metabolic-Syndrome [ti] OR Metabolism [ti] OR Metal-Metabolism [ti] OR Metaplasia [ti] OR Metatarsalgia [ti] OR Methemoglobinemia [ti] OR Metrorrhagia [ti] OR Mevalonate-Kinase-Deficiency [ti] OR Microalbuminuria [ti] OR Microcephaly [ti] OR Micrognathism [ti] OR Microinflammation [ti] OR Micronuclei [ti] OR Microphthalmos [ti] OR Microsatellite-Instability [ti] OR Microscopic-Polyangiitis [ti] OR Microsporidiosis [ti] OR Microstomia [ti] OR Microvascular-Angina [ti] OR Migraine* [ti] OR Miliaria [ti] OR Milk-Hypersensitivity [ti] OR Milk-Sickness [ti] OR Mink-Viral-Enteritis [ti] OR Miosis [ti] OR Mite-Infestation* [ti] OR Mitochondrial-Encephalomyopath* [ti] OR Mitochondrial-Myopath* [ti] OR Mitral-Valve-Insufficiency [ti] OR Mitral-Valve-Prolapse [ti] OR Mixed-Tumor* [ti] OR Molluscum-Contagiosum [ti] OR Monieziasis [ti] OR Monilethrix [ti] OR Monkeypox [ti] OR Monoclonal-Gammopathy [ti] OR Mononeuropath* [ti] OR Morning-Sickness [ti] OR Morphine-Dependence [ti] OR Motion-Sickness [ti]

OR Mouth-Breathing [ti] OR Mucinoses [ti] OR Mucinosis [ti] OR Mucocele [ti] OR Mucolipidoses [ti] OR Mucopolysaccharidoses [ti] OR Mucopolysaccharidosis [ti] OR Mucormycosis [ti] OR Mucositis [ti] OR Multicystic-Dysplastic-Kidney [ti] OR Multiple-Acyl-Coenzyme-A-Dehydrogenase-Deficiency [ti] OR Multiple-Carboxylase-Deficiency [ti] OR Multiple-Chemical-Sensitivity [ti] OR Multiple-Myeloma [ti] OR Multiple-Organ-Failure* [ti] OR Multiple-Pulmonary-Nodules [ti] OR Multiple-System-Atrophy [ti] OR Mumps [ti] OR Muscle-Cramp* [ti] OR Muscle-Hypertonia [ti] OR Muscle-Hypotonia [ti] OR Muscle-Rigidity [ti] OR Muscle-Spasticity [ti] OR Muscle-Weakness [ti] OR Muscular-Atrophy [ti] OR Muscular-Dystroph* [ti] OR Mutism [ti] OR Myalgia [ti] OR Myasthenia-Gravis [ti] OR Mycetoma [ti] OR Mycoses [ti] OR Mycosis-Fungoides [ti] OR Mycotoxicosis [ti] OR Mydriasis [ti] OR Myelinolysis [ti] OR Myelitis [ti] OR Myelolipoma [ti] OR Myiasis [ti] OR Myocardial-Bridging [ti] OR Myocardial-Ischemia [ti] OR Myocardial-Reperfusion-Injury [ti] OR Myocardial-Stunning [ti] OR Myocarditis [ti] OR Myoclonic-Cerebellar-Dyssynergia [ti] OR Myoclonic-Epileps* [ti] OR Myoclonus [ti] OR Myoepithelioma [ti] OR Myoglobinuria [ti] OR Myokymia [ti] OR Myoma [ti] OR Myopath* [ti] OR Myopia [ti] OR Myositis [ti] OR Myotonia [ti] OR Myotonic-Dystrophy [ti] OR Myringosclerosis [ti] OR Myxedema [ti] OR Myxoma [ti] OR Myxomatosis [ti] OR Myxosarcoma [ti] OR Narcolepsy [ti] OR Nasal-Obstruction* [ti] OR Nasal-Polyp* [ti] OR Nasal-Septal-Perforation [ti] OR Nasopharyngitis [ti] OR Nausea [ti] OR Necatoriasis [ti] OR Necrobiosis-Lipoidica [ti] OR Necrobiotic-Xanthogranuloma [ti] OR Necrolytic-Migratory-Erythema [ti] OR Necrosis [ti] OR Neointima [ti] OR Neoplasia [ti] OR Neoplasm* [ti] OR Neoplastic-Cell* [ti] OR Neovascularization [ti] OR Nephritis [ti] OR Nephrocalcinosis [ti] OR Nephrogenic-Fibrosing-Dermopathy [ti] OR Nephrolithiasis [ti] OR Nephroma [ti] OR Nephropath* [ti] OR Nephrosclerosis [ti] OR Nephrosis [ti] OR Nerve-Degeneration [ti] OR Nerve-Injur* [ti] OR Nervous-System-Malformation* [ti] OR Nesidioblastosis [ti] OR Neural-Tube-Defect* [ti] OR Neuralgia [ti] OR Neurilemmoma [ti] OR Neuritis [ti] OR Neuroacanthocytosis [ti] OR Neuroaspergillosis [ti] OR Neuroaxonal-Dystroph* [ti] OR Neuroblastoma [ti] OR Neurocysticercosis [ti] OR Neurocytoma [ti] OR Neuroectodermal-Tumor* [ti] OR Neuroendocrine-Tumor* [ti] OR Neurofibroma [ti] OR Neurofibromatos* [ti] OR Neurofibrosarcoma [ti] OR Neurogenic-Bowel [ti] OR Neurogenic-Inflammation [ti] OR Neurogenic-Urinary-Bladder [ti] OR Neuroma [ti] OR Neuromyelitis-Optica [ti] OR Neuronal-Ceroid-Lipofuscinoses [ti] OR Neuropath* [ti] OR Neuroschistosomiasis [ti] OR Neurosyphilis [ti] OR Neurothekeoma [ti] OR Neutropenia [ti] OR Nevus [ti] OR Night-Blindness [ti] OR Night-Terror* [ti] OR Nocturia [ti] OR Nocturnal-Enuresis [ti] OR Nocturnal-Paroxysmal-Dystonia [ti] OR Noma [ti] OR Nondisjunction [ti] OR Nonodontogenic-Cysts [ti] OR Nonvital-Tooth [ti] OR No-Reflow-Phenomenon [ti] OR Nose-Deformities [ti] OR Nut-Hypersensitivity [ti] OR Nystagmus [ti] OR Obesity [ti] OR Obstetric-Labor-Complications [ti] OR Ochronosis [ti] OR Ocular-Hypotension [ti] OR Odontogenic-Cyst* [ti] OR Odontogenic-Tumor* [ti] OR Odontoma [ti] OR Oedema [ti] OR Oligodendroglioma [ti] OR Oligohydramnios [ti] OR Oligomenorrhea [ti] OR Oligospermia [ti] OR Oliguria [ti] OR Olivopontocerebellar-Atrophies [ti] OR Onchocerciasis [ti] OR Onycholysis [ti] OR Onychomycosis [ti] OR Oophoritis [ti] OR Open-Bite [ti] OR Ophthalmia [ti] OR Ophthalmoplegia [ti] OR Opisthorchiasis [ti] OR Optic-Atrophy [ti] OR Optic-Disk-Drusen [ti] OR Optic-Nerve-Glioma [ti] OR Optic-Neuritis [ti] OR Oral-Fistula* [ti] OR Orbital-Cellulitis [ti] OR Orbital-Myositis [ti] OR Orbital-Pseudotumor* [ti] OR Orchitis [ti] OR Oroantral-Fistula* [ti] OR Orthostatic-Intolerance [ti] OR Ossification [ti] OR Osteitis [ti] OR Osteoarthritis [ti] OR Osteoarthropath* [ti] OR Osteoblastoma [ti] OR Osteochondritis [ti] OR Osteochondrodysplasias [ti] OR Osteochondroma [ti] OR Osteochondrosis [ti] OR Osteodystrophy [ti] OR Osteogenesis-Imperfecta [ti] OR Osteolysis [ti] OR Osteoma [ti] OR Osteomalacia [ti] OR Osteomyelitis [ti] OR Osteonecrosis [ti] OR Osteopenia [ti] OR Osteopetrosis [ti] OR Osteophyte

[ti] OR Osteoporosis [ti] OR Osteosarcoma [ti] OR Osteosclerosis [ti] OR Ostertagiasis [ti] OR Otitis [ti] OR Otomycosis [ti] OR Otosclerosis [ti] OR Ovarian-Cyst* [ti] OR Overactive-Urinary-Bladder [ti] OR Overbite [ti] OR Overnutrition [ti] OR Overweight [ti] OR Oxidative-Stress [ti] OR Oxyuriasis [ti] OR Pachyonychia-Congenita [ti] OR Pain [ti] OR Pallor [ti] OR Pancreatic-Cyst* [ti] OR Pancreatic-Fistula* [ti] OR Pancreatic-Insufficiency [ti] OR Pancreatic-Pseudocyst [ti] OR Pancreatitis [ti] OR Pancytopenia [ti] OR Panniculitis [ti] OR Panuveitis [ti] OR Papilledema [ti] OR Papilloma [ti] OR Paracoccidioidomycosis [ti] OR Paraganglioma [ti] OR Paragonimiasis [ti] OR Parakeratosis [ti] OR Paralyses [ti] OR Paralysis [ti] OR Paraneoplastic [ti] OR Paraparesis [ti] OR Paraphimosis [ti] OR Paraplegia [ti] OR Paraproteinemias [ti] OR Parapsoriasis [ti] OR Parasitemia [ti] OR Parasomnias [ti] OR Parasystole [ti] OR Paratuberculosis [ti] OR Paresis [ti] OR Paresthesia [ti] OR Paronychia [ti] OR Parotitis [ti] OR Paroxysmal-Hemicrania [ti] OR Pars-Planitis [ti] OR Pasteurellosis [ti] OR Peanut-Hypersensitivity [ti] OR Pediatric-Obesity [ti] OR Pelger-Huet-Anomaly [ti] OR Peliosis-Hepatis [ti] OR Pellagra [ti] OR Pelvic-Organ-Prolapse [ti] OR Pemphigoid [ti] OR Pemphigus [ti] OR Penile-Induration [ti] OR Periapical-Granuloma* [ti] OR Periarthritis [ti] OR Pericardial-Effusion [ti] OR Pericarditis [ti] OR Pericoronitis [ti] OR Peri-Implantitis [ti] OR Perinephritis [ti] OR Periodontal-Atrophy [ti] OR Periodontal-Attachment-Loss [ti] OR Periodontal-Cyst* [ti] OR Periodontal-Pocket [ti] OR Periodontitis [ti] OR Periostitis [ti] OR Peritonitis [ti] OR Periventricular-Nodular-Heterotopia [ti] OR Persistent-Hyperplastic-Primary-Vitreous [ti] OR Persistent-Vegetative-State [ti] OR Peste-des-Petits-Ruminants [ti] OR Phaeohyphomycosis [ti] OR Phantom-Limb [ti] OR Pharyngitis [ti] OR Phencyclidine-Abuse* [ti] OR Phenylketonuria* [ti] OR Pheochromocytoma [ti] OR Phimosis [ti] OR Phlebitis [ti] OR Photophobia [ti] OR Phyllodes-Tumor [ti] OR Piebaldism [ti] OR Piedra [ti] OR Pilomatrixoma [ti] OR Pilonidal-Sinus [ti] OR Pinealoma [ti] OR Pinguecula [ti] OR Pituitary-ACTH-Hypersecretion [ti] OR Pituitary-Apoplexy [ti] OR Pityriasis [ti] OR Placenta [ti] OR Placental-Insufficiency [ti] OR Plagiocephaly [ti] OR Plague [ti] OR Plasma-Cell-Granuloma* [ti] OR Plasmacytoma [ti] OR Platelet-Storage-Pool-Deficiency [ti] OR Platybasia [ti] OR Pleural-Effusion [ti] OR Pleurisy [ti] OR Pleurodynia [ti] OR Pleuropneumonia [ti] OR Pneumatosis-Cystoides-Intestinalis [ti] OR Pneumocephalus [ti] OR Pneumoconiosis [ti] OR Pneumonia [ti] OR Pneumopericardium [ti] OR Pneumoperitoneum [ti] OR Pneumorrhachis [ti] OR Pneumothorax [ti] OR Poliomyelitis [ti] OR Polyarteritis-Nodosa [ti] OR Polychondritis [ti] OR Polycystic-Kidney [ti] OR Polycythemia [ti] OR Polydactyly [ti] OR Polydipsia [ti] OR Polyendocrinopathies [ti] OR Polyhydramnios [ti] OR Polymyalgia-Rheumatica [ti] OR Polymyositis [ti] OR Polyneuropathies [ti] OR Polyps [ti] OR Polyradiculopathy [ti] OR Polyuria [ti] OR Popliteal-Cyst* [ti] OR Porokeratosis [ti] OR Poroma [ti] OR Porphyria* [ti] OR Port-Wine-Stain [ti] OR Positive-Pressure-Respiration [ti] OR Posterior-Tibial-Tendon-Dysfunction [ti] OR Post-Exercise-Hypotension [ti] OR Postoperative-Complications [ti] OR Postoperative-Nausea [ti] OR postoperative-vomiting [ti] OR Postpartum-Thyroiditis [ti] OR Potassium-Deficiency [ti] OR Pouchitis [ti] OR Precancerous [ti] OR Precocious-Puberty [ti] OR Prediabetic-State [ti] OR Pre-Eclampsia [ti] OR Pre-Excitation [ti] OR Pregnancy-Complications [ti] OR Pregnancy-in-Diabetics [ti] OR Prehypertension [ti] OR Preleukemia [ti] OR Premature-Aging [ti] OR Premature-Birth [ti] OR Premature-Ejaculation [ti] OR Premature-Obstetric-Labor [ti] OR Prenatal-Injur* [ti] OR Presbycusis [ti] OR Presbyopia [ti] OR Priapism [ti] OR Primary-Dysautonomias [ti] OR Primary-Graft-Dysfunction* [ti] OR Primary-Myelofibrosis [ti] OR Primary-Ovarian-Insufficiency [ti] OR Proctitis [ti] OR Proctocolitis [ti] OR Progeria [ti] OR Prognathism [ti] OR Prolactinoma [ti] OR Prolonged-Pregnancy [ti] OR Propionic-Acidemia [ti] OR Prosopagnosia [ti] OR Prostatism [ti] OR Prostatitis [ti] OR Prosthesis-Failure* [ti] OR Protein-C-Deficiency [ti] OR Protein-Deficiency [ti] OR Protein-S-Deficiency [ti] OR Protein-Energy-Malnutrition [ti] OR Protein-Losing-

Enteropathies [ti] OR Proteinuria [ti] OR Proteostasis-Deficiencies [ti] OR Protoporphyria [ti] OR Prurigo [ti] OR Pruritus [ti] OR Pseudobulbar-Palsy [ti] OR Pseudohypoaldosteronism [ti] OR Pseudohypoparathyroidism [ti] OR Pseudolymphoma [ti] OR Pseudomyxoma-Peritonei [ti] OR Pseudophakia [ti] OR Pseudorabies [ti] OR Pseudotumor-Cerebri [ti] OR Pseudoxanthoma-Elasticum [ti] OR Psittacosis [ti] OR Psoriasis [ti] OR Psychomotor-Agitation [ti] OR Psychoses [ti] OR Pterygium [ti] OR Pubic-Symphysis-Diastasis [ti] OR Pudendal-Neuralgia [ti] OR Pulmonary-Alveolar-Proteinosis [ti] OR Pulmonary-Aspergillosis [ti] OR Pulmonary-Atelectasis [ti] OR Pulmonary-Atresia [ti] OR Pulmonary-Blastoma [ti] OR Pulmonary-Embolism [ti] OR Pulmonary-Emphysema [ti] OR Pulmonary-Eosinophilia [ti] OR Pulmonary-Nodule* [ti] OR Pulmonary-Sclerosing-Hemangioma [ti] OR Pulmonary-Valve-Insufficiency [ti] OR Pulpitis [ti] OR Pure-Autonomic-Failure [ti] OR Purine-Pyrimidine-Metabolism [ti] OR Purpura [ti] OR Pyelitis [ti] OR Pyelonephritis [ti] OR Pyoderma [ti] OR Pyometra [ti] OR Pyomyositis [ti] OR Pyonephrosis [ti] OR Pythiosis [ti] OR Pyuria [ti] OR Quadriplegia [ti] OR Rabies [ti] OR Radiation-Pneumonitis [ti] OR Radicular-Cyst* [ti] OR Radiculopathy [ti] OR Ranula [ti] OR Reactive-Oxygen-Species [ti] OR Rectal-Fistula [ti] OR Rectal-Prolapse [ti] OR Rectocele [ti] OR Rectovaginal-Fistula [ti] OR Recurrence [ti] OR Red-Cell-Aplasia [ti] OR Reflex-Sympathetic-Dystrophy [ti] OR Refractive-Errors [ti] OR Renal-Aminoacidurias [ti] OR Renal-Artery-Obstruction [ti] OR Renal-Colic [ti] OR Renal-Injury [ti] OR Renal-Insufficiency [ti] OR Renal-Osteodystrophy [ti] OR Renal-Tubular-Transport [ti] OR Reperfusion-Injury [ti] OR Respiratory-Aspiration [ti] OR Respiratory-Hypersensitivity [ti] OR Respiratory-Insufficiency [ti] OR Respiratory-Paralysis [ti] OR Respiratory-Sounds [ti] OR Respiratory-Tract-Fistula [ti] OR Restenosis [ti] OR Reticulocytosis [ti] OR Retinal-Artery-Occlusion [ti] OR Retinal-Degeneration [ti] OR Retinal-Detachment [ti] OR Retinal-Drusen [ti] OR Retinal-Neovascularization [ti] OR Retinal-Perforations [ti] OR Retinal-Telangiectasis [ti] OR Retinal-Vein-Occlusion [ti] OR Retinitis [ti] OR Retinoblastoma [ti] OR Retinopathy [ti] OR Retinoschisis [ti] OR Retrognathia [ti] OR Retrograde-Degeneration [ti] OR Retropneumoperitoneum [ti] OR Rh-Isoimmunization [ti] OR Rhabdoid-Tumor* [ti] OR Rhabdomyolysis [ti] OR Rhabdomyoma [ti] OR Rhabdomyosarcoma [ti] OR Rheumatic-Nodule* [ti] OR Rheumatoid-Nodule* [ti] OR Rhinitis [ti] OR Rhinophyma [ti] OR Rhinoscleroma [ti] OR Rhinosporidiosis [ti] OR Riboflavin-Deficiency [ti] OR Rickets [ti] OR Rigor-Mortis [ti] OR Rinderpest [ti] OR Root-Caries [ti] OR Root-Resorption [ti] OR Rosacea [ti] OR Rubella [ti] OR Rupture)

(Expos* [ti] OR induce [ti] OR induced [ti] OR induces [ti] OR incarceration [ti] OR occupation* [ti] OR pathogen* [ti] OR pollut* [ti] OR poverty [ti] OR socioeconomic [ti] OR worker*) AND (Sacroiliitis [ti] OR Salivary-Duct-Calculi [ti] OR Salivary-Gland-Calculi [ti] OR Salivary-Gland-Fistula [ti] OR Salpingitis [ti] OR Sarcocystosis [ti] OR Sarcoidosis [ti] OR Sarcoma [ti] OR Sarcopenia [ti] OR Scabies [ti] OR Scalp-Dermatoses [ti] OR Schistosomiasis [ti] OR Sciatica [ti] OR Scleredema-Adultorum [ti] OR Sclerema-Neonatorum [ti] OR Scleritis [ti] OR Scleroderma [ti] OR Scleromyxedema [ti] OR Sclerosis [ti] OR Scoliosis [ti] OR Scorpion-Sting* [ti] OR Scotoma [ti] OR Scrapie [ti] OR Scrub-Typhus [ti] OR Scurvy [ti] OR Seizures [ti] OR Seminoma [ti] OR Sepsis [ti] OR Septic-Shock [ti] OR Seroma [ti] OR Serositis [ti] OR Sertoli-Cell-Tumor* [ti] OR Sertoli-Leydig-Cell-Tumor [ti] OR Serum-Sickness [ti] OR Severe-Combined-Immunodeficiency [ti] OR Severe-Dengue [ti] OR Sex-Chromosome-Aberrations [ti] OR Sex-Cord-Gonadal-Stromal-Tumor* [ti] OR Sexual-Dysfunction [ti] OR Shwartzman-Phenomenon [ti] OR Sialadenitis [ti] OR Sialometaplasia [ti] OR Sialorrhea [ti] OR Sickle-Cell-Trait [ti] OR Siderosis [ti] OR

Silicosis [ti] OR Silicotuberculosis [ti] OR Single-Umbilical-Artery [ti] OR Sinoatrial-Block [ti] OR Sinus-Arrest [ti] OR Sinus-Pericranii [ti] OR Sinusitis [ti] OR Situs-Inversus [ti] OR Skull-Fracture* [ti] OR Sleep-Apnea [ti] OR Sleep-Bruxism [ti] OR Sleep-Deprivation [ti] OR Sleep-Paralysis [ti] OR Slipped-Capital-Femoral-Epiphyses [ti] OR Smallpox [ti] OR Smooth-Muscle-Tumor* [ti] OR Snake-Bite* [ti] OR Sneezing [ti] OR Snoring [ti] OR Somatostatinoma [ti] OR Somnambulism [ti] OR Space-Motion-Sickness [ti] OR Sparganosis [ti] OR Spasm [ti] OR Spasms [ti] OR Spastic-Paraplegia [ti] OR Spermatic-Cord-Torsion [ti] OR Spermatocele [ti] OR Sphenoid-Sinusitis [ti] OR Spherocytosis [ti] OR Sphincter-of-Oddi-Dysfunction [ti] OR Sphingolipidoses [ti] OR Spider-Bite* [ti] OR Spina-Bifida [ti] OR Spinal-Cord-Compression [ti] OR Spinal-Cord-Injur* [ti] OR Spinal-Cord-Ischemia [ti] OR Spinal-Curvature* [ti] OR Spinal-Dysraphism [ti] OR Spinal-Muscular-Atrophies-of-Childhood [ti] OR Spinal-Osteophytosis [ti] OR Spinocerebellar-Ataxias [ti] OR Spinocerebellar-Degeneration* [ti] OR Splenomegaly [ti] OR Splenosis [ti] OR Spondylarthritis [ti] OR Spondylarthropathies [ti] OR Spondylitis [ti] OR Spondylolisthesis [ti] OR Spondylolysis [ti] OR Spondylosis [ti] OR Sporotrichosis [ti] OR Sprue [ti] OR Starvation [ti] OR Status-Asthmaticus [ti] OR Status-Epilepticus [ti] OR Steatitis [ti] OR Steatorrhea [ti] OR Stenosis [ti] OR Steroid-Metabolism [ti] OR Stings [ti] OR Stomach-Volvulus [ti] OR Stomatitis [ti] OR Strabismus [ti] OR Striae-Distensae [ti] OR Striatonigral-Degeneration [ti] OR Stricture* [ti] OR Stroke [ti] OR Strongyloidiasis [ti] OR Stupor [ti] OR Stuttering [ti] OR Subacute-Combined-Degeneration [ti] OR Subacute-Sclerosing-Panencephalitis [ti] OR Subcutaneous-Emphysema [ti] OR Subdural-Effusion [ti] OR Substance-Abuse* [ti] OR Sudden-Death [ti] OR Sudden-Infant-Death* [ti] OR Sulfhemoglobinemia [ti] OR Sunburn [ti] OR Supernumerary-Tooth [ti] OR Suppuration [ti] OR Supranuclear-Palsy [ti] OR Surgical-Shock [ti] OR Surgical-Wound-Dehiscence [ti] OR Sweating [ti] OR Swine-Erysipelas [ti] OR Syncope [ti] OR Syndactyly [ti] OR Syndrome* [ti] OR Synkinesis [ti] OR Synostosis [ti] OR Synovial-Cyst* [ti] OR Synovitis [ti] OR Syphilis [ti] OR Syringoma [ti] OR Syringomyelia [ti] OR Systolic-Murmurs [ti] OR Tabes-Dorsalis [ti] OR Tachycardia [ti] OR Tachypnea [ti] OR Taeniasis [ti] OR Takayasu-Arteritis [ti] OR Takotsubo-Cardiomyopathy [ti] OR Tarlov-Cysts [ti] OR Tauopathies [ti] OR Tauopathy [ti] OR TDP-43-Proteinopathies [ti] OR Telangiectasia [ti] OR Telangiectasis [ti] OR Tendinopath* [ti] OR Tendon-Entrapment [ti] OR Tennis-Elbow [ti] OR Tenosynovitis [ti] OR Teratocarcinoma* [ti] OR Teratogenesis [ti] OR Teratoma [ti] OR Testicular-Hydrocele* [ti] OR Tetanus [ti] OR Tetany [ti] OR Tetralogy-of-Fallot [ti] OR Thalassemia [ti] OR Thecoma [ti] OR Theileriasis [ti] OR Thiamine-Deficiency [ti] OR Thinness [ti] OR Thrombasthenia [ti] OR Thromboangiitis-Obliterans [ti] OR Thrombocythemia [ti] OR Thrombocytopenia [ti] OR Thrombocytosis [ti] OR Thromboembolism [ti] OR Thrombophilia [ti] OR Thrombophlebitis [ti] OR Thrombosis [ti] OR Thrombotic-Microangiopathies [ti] OR Thymoma [ti] OR Thyroglossal-Cyst* [ti] OR Thyroid-Crisis [ti] OR Thyroid-Dysgenesis [ti] OR Thyroid-Nodule* [ti] OR Thyroiditis [ti] OR Thyrotoxicosis [ti] OR Tick-Bite* [ti] OR Tick-Infestation* [ti] OR Tick-Paralysis [ti] OR Tick-Toxicoses [ti] OR Tics [ti] OR Tinea [ti] OR Tinnitus [ti] OR Tissue-Adhesions [ti] OR T-Lymphocytopenia [ti] OR Tonic-Pupil [ti] OR Tonsillitis [ti] OR Tooth-Abrasion [ti] OR Tooth-Ankylosis [ti] OR Tooth-Attrition [ti] OR Tooth-Avulsion [ti] OR Tooth-Demineralization [ti] OR Tooth-Discoloration* [ti] OR Tooth-Erosion [ti] OR Tooth-Fracture* [ti] OR Tooth-Injur* [ti] OR Tooth-Loss [ti] OR Tooth-Migration [ti] OR Tooth-Mobility [ti] OR Tooth-Resorption [ti] OR Tooth-Wear [ti] OR Toothache* [ti] OR Torsades-de-Pointes [ti] OR Torticollis [ti] OR Toxascariasis [ti] OR Toxemia [ti] OR Toxic-Shock [ti] OR Toxocariasis [ti] OR Toxoplasmosis [ti] OR Tracheitis [ti] OR Tracheobronchomalacia [ti] OR Tracheobronchomegaly [ti] OR Tracheoesophageal-Fistula [ti] OR Tracheomalacia [ti] OR Trachoma [ti] OR Transient-Tachypnea [ti] OR Translocation [ti] OR Transposition-of-Great-Vessels [ti] OR Trauma [ti] OR Traumatic-Shock [ti] OR Tremor* [ti] OR Trichiasis

[ti] OR Trichinellosis [ti] OR Trichomonas-Vaginitis [ti] OR Trichosporonosis [ti] OR Trichostrongyloidiasis [ti] OR Trichostrongylosis [ti] OR Trichuriasis [ti] OR Tricuspid-Atresia [ti] OR Tricuspid-Valve-Insufficiency [ti] OR Trigeminal-Autonomic-Cephalalgias [ti] OR Trigeminal-Neuralgia [ti] OR Trilogy-of-Fallot [ti] OR Trismus [ti] OR Trisomy [ti] OR Trombiculiasis [ti] OR Trophoblastic-Tumor* [ti] OR Trypanosomiasis [ti] OR Tubal-Pregnancy [ti] OR Tuberculoma [ti] OR Tuberculosis [ti] OR Tularemia [ti] OR Tungiasis [ti] OR Tympanic-Membrane-Perforation [ti] OR Typhlitis [ti] OR Typhus [ti] OR Tyrosinemias [ti] OR Ulcer* [ti] OR Unconsciousness [ti] OR Uniparental-Disomy [ti] OR Upper-Extremity-Deformities [ti] OR Urachal-Cyst* [ti] OR Uraemia [ti] OR Uremia [ti] OR Ureteral-Calculi [ti] OR Ureteral-Obstruction* [ti] OR Ureterocele [ti] OR Ureterolithiasis [ti] OR Urethral-Obstruction* [ti] OR Urethritis [ti] OR Urinary-Bladder-Calculi [ti] OR Urinary-Bladder-Fistula* [ti] OR Urinary-Bladder-Neck-Obstruction* [ti] OR Urinary-Calculi [ti] OR Urinary-Fistula [ti] OR Urinary-Incontinence [ti] OR Urinary-Retention [ti] OR Urinoma [ti] OR Urolithiasis [ti] OR Urticaria [ti] OR Urticaria-Pigmentosa [ti] OR Uterine-Cervical-Erosion [ti] OR Uterine-Cervical-Incompetence [ti] OR Uterine-Cervicitis [ti] OR Uterine-Inertia [ti] OR Uterine-Inversion [ti] OR Uterine-Perforation* [ti] OR Uterine-Prolapse [ti] OR Uterine-Retroversion [ti] OR Uveitis [ti] OR Vaccinia [ti] OR Vaginal-Discharge* [ti] OR Vaginal-Fistula* [ti] OR Vaginismus [ti] OR Vaginitis [ti] OR Vaginosis [ti] OR Varicocele [ti] OR Varicose-Veins [ti] OR Vasa-Previa [ti] OR Vascular-Calcification [ti] OR Vascular-Fistula [ti] OR Vascular-Malformations [ti] OR Vascular-Resistance [ti] OR Vascular-Stiffness [ti] OR Vascular-System-Injur* [ti] OR Vasculitis [ti] OR Vasoconstriction [ti] OR Vasoplegia [ti] OR Vasospasm [ti] OR Vein-of-Galen-Malformations [ti] OR Velopharyngeal-Insufficiency [ti] OR Venous-Insufficiency [ti] OR Venous-Thromboembolism* [ti] OR Ventilator-Induced-Lung-Injury [ti] OR Ventricular-Dysfunction* [ti] OR Ventricular-Fibrillation* [ti] OR Ventricular-Outflow-Obstruction* [ti] OR Ventricular-Premature-Complexes [ti] OR Ventricular-Remodeling [ti] OR Vertebral-Artery-Dissection [ti] OR Vertebrobasilar-Insufficiency [ti] OR Vertigo [ti] OR Vesico-Ureteral-Reflux [ti] OR Vesicovaginal-Fistula* [ti] OR Vesicular-Stomatitis [ti] OR Vestibular-Neuronitis [ti] OR VIRAL-Cell-Transformation [ti] OR Viremia [ti] OR Virilism [ti] OR Visceral-Prolapse [ti] OR Visna [ti] OR Vitamin-A-Deficiency [ti] OR Vitamin-B-12-Deficiency [ti] OR Vitamin-B-6-Deficiency [ti] OR Vitamin-B-Deficiency [ti] OR Vitamin-D-Deficiency [ti] OR Vitamin-E-Deficiency [ti] OR Vitamin-K-Deficiency [ti] OR Vitiligo [ti] OR Vitreoretinopathy [ti] OR Vitreous-Detachment [ti] OR Vocal-Cord-Dysfunction [ti] OR Vocal-Cord-Paralysis [ti] OR Vomiting [ti] OR Vulvar-Lichen-Sclerosus [ti] OR Vulvar-Vestibulitis [ti] OR Vulvitis [ti] OR Vulvodynia [ti] OR Vulvovaginitis [ti] OR Waldenstrom-Macroglobulinemia [ti] OR Wallerian-Degeneration [ti] OR Wandering-Spleen [ti] OR Warts [ti] OR Water-Electrolyte-Imbalance [ti] OR Wegener-Granulomatosis [ti] OR Wernicke-Encephalopathy [ti] OR Wet-Macular-Degeneration [ti] OR Wheat-Hypersensitivity [ti] OR Whooping-Cough [ti] OR Wilms-Tumor [ti] OR Xanthogranuloma* [ti] OR Xanthomatosis [ti] OR Xeroderma-Pigmentosum [ti] OR Xerophthalmia [ti] OR Xerostomia [ti] OR Yang-Deficiency [ti] OR Yaws [ti] OR Yin-Deficiency [ti] OR Zenker-Diverticulum [ti] OR Zoonoses [ti] OR Zoster-Sine-Herpete [ti] OR Zygomycosis [ti])

1C3. Linking Terms Used to Extract Causes from Titles

There were millions of Title phrases that had to be evaluated for potential causes. Only the highest frequency phrases could be inspected visually. To access the lower frequency terms, a number of linking terms were identified.

The linking terms were obtained through visual inspection of many records containing causes in the Titles, and identifying those that appeared frequently with the causes. These linking terms included: -induced; caused by; induced by; -contaminated; exposure to; exposure(s) [at end of phrase]; exposed to; poisoning [at end]; workers [at end]; -exposed [at end]; -related; -associated; -infected; abuse*; toxicity. The inclusion of the term 'workers' was to identify industries that were noticeable contributors to disease. The phrases that included the linking terms had to be separated from the linking terms to identify the specific causes and include them in the software matrices. Other linking terms were virus* and generic bacterial headings, but these did not have to be separated from the phrases.

1C4. Linking Terms Used to Extract Diseases from Titles

The linking terms were obtained through visual inspection of many records containing diseases in the Titles, and identifying those that appeared frequently with the diseases. These linking terms included: disease; syndrome; infection; cancer; *toxicity; *opathy. Since specific diseases did not always appear in record Titles when the causes appeared, terms that implied damage or adverse effects were used, such as *toxicity. So, for example, with a phrase like 'cadmium toxicity', 'cadmium' would be extracted as a cause, and 'toxicity' would be listed as a 'disease'.

1C5. Generic MeSH Terms Strongly Related to Potential Causes

A number of records with MeSH term assignments either had no Qualifiers listed or insufficient Qualifiers. In addition, while the Qualifiers used for the all-Qualifier query captured a large number of causes, they were incomplete. Therefore, the high and mid-frequency MeSH terms in the MeSH tree were inspected visually, and those that appeared to be generic and cause-focused were selected as a query. The MeSH Headings that resulted in the retrieval consisted of causes, and other. Because there were no linking terms that could be used to extract only the causes MeSH Headings, the output had to be inspected visually, and those terms that appeared to be causes had to be extracted manually and validated. Mainly, the high frequency output terms were the only ones evaluated.

The following query was used to retrieve the records from Pubmed, where the first set consists of all diseases and symptoms from the MeSH tree, and the second set is the MeSH terms strongly related to causes:

([MH] is the Pubmed tag for MeSH Heading; [MH:NOEXP] is the Pubmed tag for MeSH Heading No Explode)

(Bacterial Infections and Mycoses [MH] OR Cardiovascular Diseases [MH] OR Chemically-Induced Disorders [MH] OR Congenital, Hereditary, and Neonatal Diseases and Abnormalities [MH] OR Digestive System Diseases [MH] OR Disorders of Environmental Origin [MH] OR Endocrine System Diseases [MH] OR Eye Diseases [MH] OR Female Urogenital Diseases and Pregnancy Complications [MH] OR Hemic and Lymphatic Diseases [MH] OR Immune System Diseases [MH] OR Male Urogenital Diseases [MH] OR Musculoskeletal Diseases [MH] OR Neoplasms [MH] OR Nervous System Diseases [MH] OR Nutritional and Metabolic Diseases [MH] OR Occupational Diseases [MH] OR Otorhinolaryngologic Diseases [MH]

OR Parasitic Diseases [MH] OR Pathological Conditions, Signs and Symptoms [MH] OR Respiratory Tract Diseases [MH] OR Skin and Connective Tissue Diseases [MH] OR Stomatognathic Diseases [MH] OR Virus Diseases [MH])

AND

("DRUG-RELATED SIDE EFFECTS AND ADVERSE REACTIONS" [MH:NOEXP] OR ABNORMALITIES, DRUG INDUCED [MH:NOEXP] OR ABNORMALITIES, RADIATION-INDUCED [MH:NOEXP] OR AGRICULTURAL WORKERS DISEASES [MH:NOEXP] OR AIDS RELATED OPPORTUNISTIC INFECTIONS [MH:NOEXP] OR AIR POLLUTANTS [MH:NOEXP] OR AIR POLLUTANTS, OCCUPATIONAL [MH:NOEXP] OR AIR POLLUTANTS, RADIOACTIVE [MH:NOEXP] OR AIR POLLUTION [MH:NOEXP] OR AIR POLLUTION, INDOOR [MH:NOEXP] OR AIR POLLUTION, RADIOACTIVE [MH:NOEXP] OR ALCOHOL DRINKING [MH:NOEXP] OR ALCOHOL RELATED DISORDERS [MH:NOEXP] OR ALCOHOLIC BEVERAGES [MH:NOEXP] OR ALCOHOLIC INTOXICATION [MH:NOEXP] OR ALCOHOLISM [MH:NOEXP] OR AMPHETAMINE RELATED DISORDERS [MH:NOEXP] OR AMPHETAMINES [MH:NOEXP] OR ARSENIC POISONING [MH:NOEXP] OR ASTHMA, ASPIRIN-INDUCED [MH:NOEXP] OR ASTHMA, EXERCISE-INDUCED [MH:NOEXP] OR ASTHMA, OCCUPATIONAL [MH:NOEXP] OR BEHAVIOR, ADDICTIVE [MH:NOEXP] OR BULLYING [MH:NOEXP] OR CADMIUM POISONING [MH:NOEXP] OR CARBON MONOXIDE POISONING [MH:NOEXP] OR CARBON TETRACHLORIDE POISONING [MH:NOEXP] OR CARCINOGENICITY TESTS [MH:NOEXP] OR CARCINOGENS [MH:NOEXP] OR CARCINOGENS, ENVIRONMENTAL [MH:NOEXP] OR CAUSALITY [MH:NOEXP] OR CARDIOMEGALY, EXERCISE-INDUCED [MH:NOEXP] OR CHEMICAL WARFARE AGENTS [MH:NOEXP] OR CHEMICALLY-INDUCED DISORDERS [MH:NOEXP] OR CHILD ABUSE [MH:NOEXP] OR CHILD ABUSE, SEXUAL [MH:NOEXP] OR CHOLESTEROL, DIETARY [MH:NOEXP] OR CIGUATERA POISONING [MH:NOEXP] OR COCAINE RELATED DISORDERS [MH:NOEXP] OR CYTOMEGALOVIRUS INFECTIONS [MH:NOEXP] OR DERMATITIS, OCCUPATIONAL [MH:NOEXP] OR DIET, ATHEROGENIC [MH:NOEXP] OR DIET, HIGH FAT [MH:NOEXP] OR DIETARY CARBOHYDRATES [MH:NOEXP] OR DIETARY FATS [MH:NOEXP] OR DIETARY FATS, UNSATURATED [MH:NOEXP] OR DIETARY FIBER [MH:NOEXP] OR DIETARY SUCROSE [MH:NOEXP] OR DOMESTIC VIOLENCE [MH:NOEXP] OR DRUG CONTAMINATION [MH:NOEXP] OR DRUG ERUPTIONS [MH:NOEXP] OR DRUG HYPERSENSITIVITY [MH:NOEXP] OR DRUG OVERDOSE [MH:NOEXP] OR DRUG-INDUCED LIVER INJURY [MH:NOEXP] OR DYSKINESIA, DRUG INDUCED [MH:NOEXP] OR EATING DISORDERS [MH:NOEXP] OR ENVIRONMENTAL EXPOSURE [MH:NOEXP] OR ENVIRONMENTAL ILLNESS [MH:NOEXP] OR ENVIRONMENTAL POLLUTANTS [MH:NOEXP] OR ENVIRONMENTAL POLLUTION [MH:NOEXP] OR ENVIRONMENTAL POLLUTION [MH:NOEXP] OR ESCHERICHIA COLI INFECTIONS [MH:NOEXP] OR FAST FOODS [MH:NOEXP] OR FLUORIDE POISONING [MH:NOEXP] OR FOOD ADDITIVES [MH:NOEXP] OR FOOD CONTAMINATION [MH:NOEXP] OR FOOD HYPERSENSITIVITY [MH:NOEXP] OR FOODBORNE DISEASES [MH:NOEXP] OR GAS POISONING [MH:NOEXP] OR HAZARDOUS SUBSTANCES [MH:NOEXP] OR HAZARDOUS WASTE [MH:NOEXP] OR HEARING LOSS, NOISE INDUCED [MH:NOEXP] OR HEAVY METAL POISONING, NERVOUS SYSTEM [MH:NOEXP] OR HEPATITIS A, CHRONIC [MH:NOEXP] OR HEPATITIS B, CHRONIC [MH:NOEXP] OR HEPATITIS C, CHRONIC [MH:NOEXP] OR HEROIN DEPENDENCE [MH:NOEXP] OR HERPESVIRIDAE INFECTIONS [MH:NOEXP] OR HTLV I INFECTIONS [MH:NOEXP] OR HYPERSENSITIVITY [MH:NOEXP] OR HYPERSENSITIVITY, DELAYED [MH:NOEXP] OR HYPERSENSITIVITY, IMMEDIATE [MH:NOEXP] OR IATROGENIC DISEASE [MH:NOEXP] OR INHALATION EXPOSURE [MH:NOEXP] OR IRON OVERLOAD [MH:NOEXP] OR LEAD POISONING [MH:NOEXP] OR LEAD POISONING, NERVOUS SYSTEM [MH:NOEXP] OR LEAD POISONING, NERVOUS SYSTEM, ADULT [MH:NOEXP] OR LEAD

POISONING, NERVOUS SYSTEM, CHILDHOOD [MH:NOEXP] OR LEUKEMIA, RADIATION INDUCED [MH:NOEXP] OR MANGANESE POISONING [MH:NOEXP] OR MARIJUANA ABUSE [MH:NOEXP] OR MATERNAL EXPOSURE [MH:NOEXP] OR MERCURY POISONING [MH:NOEXP] OR MERCURY POISONING, NERVOUS SYSTEM [MH:NOEXP] OR MORPHINE DEPENDENCE [MH:NOEXP] OR MPTP POISONING [MH:NOEXP] OR MUSHROOM POISONING [MH:NOEXP] OR MUTAGENICITY TESTS [MH:NOEXP] OR MUTAGENS [MH:NOEXP] OR NEOPLASMS, RADIATION INDUCED [MH:NOEXP] OR NEUROTOXICITY SYNDROMES [MH:NOEXP] OR OCCUPATIONAL DISEASES [MH:NOEXP] OR OCCUPATIONAL EXPOSURE [MH:NOEXP] OR OPIOID RELATED DISORDERS [MH:NOEXP] OR OPPORTUNISTIC INFECTIONS [MH:NOEXP] OR ORGANOPHOSPHATE POISONING [MH:NOEXP] OR PATERNAL EXPOSURE [MH:NOEXP] OR PLANT POISONING [MH:NOEXP] OR PNEUMONIA, VENTILATOR-ASSOCIATED [MH:NOEXP] OR POISONING [MH:NOEXP] OR POISONS [MH:NOEXP] OR PRENATAL EXPOSURE DELAYED EFFECTS [MH:NOEXP] OR PSYCHOSES, SUBSTANCE INDUCED [MH:NOEXP] OR RADIATION EFFECTS [MH:NOEXP] OR RADIATION INJURIES [MH:NOEXP] OR RADIOACTIVE HAZARD RELEASE [MH:NOEXP] OR RADIOACTIVE POLLUTANTS [MH:NOEXP] OR RESPIRATORY HYPERSENSITIVITY [MH:NOEXP] OR SALMONELLA FOOD POISONING [MH:NOEXP] OR SEDENTARY LIFESTYLE [MH:NOEXP] OR SHELLFISH POISONING [MH:NOEXP] OR SLEEP DEPRIVATION [MH:NOEXP] OR SLEEP DISORDERS [MH:NOEXP] OR SODIUM CHLORIDE, DIETARY [MH:NOEXP] OR SODIUM, DIETARY [MH:NOEXP] OR SOIL POLLUTANTS [MH:NOEXP] OR SOIL POLLUTANTS, RADIOACTIVE [MH:NOEXP] OR SPOUSE ABUSE [MH:NOEXP] OR STAPHYLOCOCCAL FOOD POISONING [MH:NOEXP] OR STAPHYLOCOCCAL INFECTIONS [MH:NOEXP] OR STREPTOCOCCAL INFECTIONS [MH:NOEXP] OR SUBSTANCE ABUSE, INTRAVENOUS [MH:NOEXP] OR SUBSTANCE WITHDRAWAL SYNDROME [MH:NOEXP] OR SUBSTANCE-RELATED DISORDERS [MH:NOEXP] OR TERATOGENS [MH:NOEXP] OR TOBACCO SMOKE POLLUTION [MH:NOEXP] OR TOBACCO USE DISORDER [MH:NOEXP] OR TOXICITY TESTS, CHRONIC [MH:NOEXP] OR VIRUS DISEASES [MH:NOEXP] OR VITAMIN D DEFICIENCY [MH:NOEXP] OR WATER POLLUTANTS [MH:NOEXP] OR WATER POLLUTANTS, CHEMICAL [MH:NOEXP] OR WATER POLLUTANTS, RADIOACTIVE [MH:NOEXP] OR WATER POLLUTION [MH:NOEXP] OR WATER POLLUTION, CHEMICAL [MH:NOEXP])

(return to TOC)

APPENDIX 3 – AD CONTRIBUTING FACTOR AND TREATMENT IDENTIFICATION METHODOLOGY

SDM-2. Detailed Methodology

SDM-2A. Identification of Foundational Causes of AD

SDM-2A1. Overview

This study focuses on identifying Direct (and some Indirect) AD foundational causes. It extrapolates and extends the identification techniques used in the chronic kidney disease (CKD) study (Kostoff and Patel, 2015) and in the eBook on identifying foundational causes for 'all' diseases (Kostoff, 2015). In the CKD study, approximately 900 direct and indirect potential foundational causes of CKD were identified (as well as direct and indirect treatments), and in the eBook, approximately 800 potential pervasive foundational causes of disease were identified ('pervasive' meant that the foundational cause listed contributed to some threshold number of different diseases).

The present study had two main components, with a different approach and different search engine for each component. The earlier component involved 1) using a novel targeted query to retrieve records with high probability of containing AD foundational causes, and then 2) performing a visual inspection (reading) of the retrieved records. The later component involved retrieving all the records in the AD core literature, then using advanced text mining techniques to extract phrases from text fields (and MeSH terms from the MeSH field) that had high probability of being foundational causes.

SDM-2A2. Database/ Search Engine Selection

The first step in designing and developing a specific query for retrieving records is identifying the databases(s) and search engine(s) that will be used in the retrieval process, since the query format has to be tailored to the database and search engine characteristics. Medline was selected as the database to be used, since it is the main repository of records from the premier biomedical journals. The Thomson Reuters version of the Medline search engine was used for the initial visual inspection component of the AD study, since the Thomson search engine had the proximity search capability compatible with query terms. The Pubmed version of the Medline search engine was used for the later 'streamlined' component of the AD study, since the phrase extraction approach did not require proximity searching.

SDM-2A3. Visual Inspection Component

To define candidate query terms, an AD core literature consisting of about 100,000 Medline records was downloaded and examined. The higher frequency MeSH terms associated with the AD core literature records were examined manually, and those MeSH terms that appeared to relate to foundational causes were evaluated for relevance. Nominally, ten records that contained each candidate causes MeSH term were examined, and if relevance was about 70% or beyond, the MeSH term was selected. In borderline cases, more MeSH terms were sampled until definitive conclusions could be drawn. Relevant does not mean unanimity or consensus was achieved for causes. Non-agreement with the majority could have been attributable to poor research, research with a pre-determined agenda (e.g., Kostoff, 2015, 2016), or selection of a 'window' in parameter space different from where the cause was operable. But, if cause was found operable in a few of the sampled papers for a given MeSH term, the term was deemed sufficiently important to select for the query.

These higher frequency MeSH terms were then matrixed with all MeSH terms in the retrieval. Lower frequency MeSH term candidates were identified through strong co-occurrence with the higher frequency terms, and the lower frequency terms were subsequently validated. Then, a separate database was generated consisting of all the records that included these high and low frequency selected MeSH terms. In this new database, the higher frequency Abstract phrases were examined, and those that appeared to relate to potential causes were evaluated for relevance. A similar procedure to that used for causes MeSH term selection was followed. The higher frequency Abstract phrases, and some generic Abstract phrases related to causes (e.g., expos*, induc*, etc), were matrixed with all Abstract phrases to identify lower frequency phrase candidates through strong co-occurrence.

Eventually, all the MeSH terms were read and examined, and a few low frequency terms that were missed with the co-occurrence procedure were added to the list. The same was not possible with the Abstract phrases. While there were thousands of MeSH terms (readable, although visually intensive), there were millions of Abstract phrases.

As stated in the Introduction, only foundational causes were evaluated in this study. There were six main types of foundational causes: Lifestyle, Iatrogenic, Biotoxic, Occupational/Environmental, Psychosocial/Socioeconomic, and Genetics. Since the purpose of this study is to identify specific causes to eliminate in order to prevent/halt/reverse AD, and since relatively little can be done at this time to alter the genetics foundational causes, the genetics causes were not included in the final queries.

The overall query structure was of the generic form [Cause][Produces][Symptom]. Two of the three would be specified in the query, directly or implicitly, and the retrieval would provide the third. Examples from causes query:

a. Cause near Produces: steroid-induc* or diet-induc* OR antibiotic near/1 cause*. These are generic or specific members of classes of potential causes in proximity to Produces-type terms. The classes tend to be drugs, diets, chemicals, radiation sources, etc. The Produces-type terms are necessary since drugs, diets, etc can be either beneficial or harmful, depending on circumstances (e.g., a chemotherapeutic drug can be helpful for treating cancer, but may also produce cognitive decline).

b. Produces near Symptom: cause* near/5 "cognitive decline" NOT "cognitive decline cause*"

c. Cause near Symptom: *Bacterium or pentachloro* in title, with either Symptom in title or in MeSH. If Abstracts are searched, stronger proximity conditions are required; e.g., *Bacterium near/5 Symptom. Unlike case a) above, in this case the causes are specific members of classes of potential causes that usually don't have beneficial effects, and therefore don't require proximity to causes-like terms; the causative nature is implied by the substance.

Note on the above. The model used was [cause-produce-symptom], but a somewhat broader form could be: [cause-produce-adverse effects], of which Symptom is one way of describing an adverse effect. Thus, 'toxic*' or 'adverse effect*', or 'harm*' in the Title by itself, along with the Symptom in the Title or MeSH tends to be accompanied by the cause and the effect it has.

Additionally, many research articles addressing causes use the language [cause-activates/inhibits/blocks-signaling pathway(s)] (e.g., "MicroRNA-222 promotes tumorigenesis via targeting DKK2 and activating the Wnt/beta-catenin signaling pathway"). The signaling pathways were

not used as part of the queries in this study, but a future more comprehensive and well-resourced study could include the signaling pathways in the queries; their incorporation would be straight-forward. Many research papers, especially at the more fundamental biological level, may not mention diseases or symptoms, but are written in the language of effects on signaling pathways, and these papers could be accessed by the appropriately-written queries. To close the loop in this case, the link between altered signalling pathway and either AD or its surrogate endpoints would have to be established.

The final query used is shown in SDM-2A - Appendix 1. The Thomson Medline AD core literature (from 1994-2014) consisted of 76663 records, and intersection of the query terms with this literature yielded 10,733 records. The most recent 5,000 were inspected visually, and the relevant foundational causes were extracted.

SDM-2A4. Streamlined Component

SDM-2A4a. Overview

An AD core literature consisting of 99,610 records was downloaded from Pubmed on 25 April 2015. Three streamlined sub-components were applied to this downloaded literature to extract AD foundational causes.

The first sub-component used only MeSH Qualifiers to filter downloaded records and extract potential foundational causes. The second sub-component used MeSH terms (relatively unambiguously related to foundational causes) to filter downloaded records and extract potential foundational causes. The third sub-component used text terms (applied to the Title and Abstract fields) to filter downloaded records and extract potential foundational causes. The results of the Visual Inspection component and the Streamlined component were integrated to produce the final AD foundational causes, as shown in the taxonomy of SDM-3.

SDM-2A4b. MeSH-Based Approach

SDM-2A4b1. MeSH Qualifiers Approach

An offshoot of the MeSH Qualifier concept was used for identifying foundational causes. MeSH Headings have a number of Qualifiers associated with them to allow focus on items of interest. Thus, the MeSH term Cadmium/ toxicity allows records to be retrieved related to the toxicity of Cadmium. These MeSH Qualifiers may be perceived as linking terms to the MeSH Headings, allowing for 'surgical' extraction of MeSH Headings that meet desired criteria. Thus, if MeSH Qualifiers strongly related to foundational causes can be identified, they can be used to identify MeSH Headings that are potential foundational causes of disease.

There are 83 topical MeSH Qualifiers used for indexing and cataloging in conjunction with MeSH Heading descriptors in Pubmed (as of 2015). All 83 were examined in more or less detail for applicability to identifying foundational causes of disease. For the initial Visual Inspection approach query, three were selected as producing relevant results when used in isolation: *chemically induced, toxicity, poisoning*.

The Streamlined approach was performed one year after the Visual Inspection approach, with one year's experience working with the selected MeSH qualifiers. The MeSH qualifiers were re-

examined for the Streamlined approach, and four were selected (after extensive validation) as producing highly relevant results when used in isolation: *adverse effects, toxicity, pathogenicity, poisoning*. A few limited combinations of the remaining MeSH Qualifiers were examined for the Streamlined approach, but none were deemed to have sufficient relevance.

All MeSH terms that contained at least one of these qualifiers were extracted, and the related records examined for potential foundational causes. While this MeSH Qualifier linking approach was developed for, and applied to, potential foundational causes, it can be easily modified for identifying potential treatments, identifying potential biomarkers, identifying potential mechanisms, etc.

SDM-2A4b2. MeSH Headings Approach

MeSH Headings related relatively unambiguously to foundational causes were identified two ways. First, results from past studies were examined, especially (Kostoff and Patel, 2015; Kostoff, 2015), and relevant MeSH Headings were extracted. Second, a few of the most unambiguous MeSH terms identified from past studies were entered into Pubmed as query terms, and all the MeSH terms in the resultant retrieval (i.e., those that co-occurred with the entry MeSH terms) were examined for relevance. The final list of relevant MeSH terms (SDM-2A - Appendix 2) was intersected with the total list of MeSH terms in the retrieved database, and the resulting records were examined for potential AD foundational causes. Again, while this focused MeSH Heading approach was developed for identifying potential foundational causes, it could (with some work) be adapted to identifying potential treatments, potential biomarkers, potential mechanisms, etc.

SDM-2A4c. Text-Based Approach

SDM-2A4c1. Title Linking Phrases Approach

Because of MeSH terms' limitations (not all Medline records have MeSH descriptors, not all MeSH terms are included in those records that have MeSH terms, not all MeSH descriptors used have appropriate Qualifiers attached. etc), a text-based approach for identifying causes was added. Because of 1) the large number of phrases in a record's Abstract compared to the Title, and 2) computer storage and software limitations, the bulk of the analysis was performed on the Title phrases. A more limited analysis was performed on the Abstract phrases, and is shown in Section SDM-2A4c3 - Abstract Linking Phrases Approach.

There were millions of Title phrases that had to be evaluated for potential causes. Only the highest frequency phrases could be inspected visually. To access the lower frequency terms, a number of linking terms were identified.

The linking terms were generated through visually inspecting many records containing foundational causes in the Titles, and identifying those terms that appeared frequently with the foundational causes. These linking terms include: -induced; caused by; induced by; -contaminated; exposure to; exposure(s) [at end of phrase]; exposed to; poisoning [at end]; -exposed [at end]; -related; -associated; -infected; abuse*; toxicity. The phrases that included the linking terms eventually had to be separated from the linking terms to identify the specific foundational causes. Other linking terms were virus* and generic bacterial headings, but these did not have to be separated from the phrases.

SDM-2A4c2. Title Dot Product Approach

Finally, potential foundational causes from myriad other sources (including past foundational causes studies, government-approved lists of toxic substances, MeSH-derived causes, etc) were intersected with the full list of Title phrases, and added to the potential foundational causes identified in the Linking Phrases approach.

While the Title phrase linking terms were developed specifically for identifying causes, a similar approach could be used to develop linking terms for identifying potential treatments, potential biomarkers, or potential mechanisms. Moreover, there could be substantial benefits gained by using Abstracts for phrase generation rather than Titles, and even full-text rather than Abstracts. While use of proximity queries with the linking terms in the Title were not required, they would be required for use in Abstracts or full-text. Adding proximity capability would be a minor modification to the form of the query developed below. The major issue would be switching to a database search engine that had the capability of proximity searching.

SDM-2A4c3 - Abstract Linking Phrases Approach

Given the size and breadth of Abstracts relative to Titles, most of the linking terms used to extract causes from the Title were relatively inefficient in extracting foundational causes from the Abstract. Variants of induc* and expos* were used to link to potential foundational causes in Abstract records, and these extracted terms received the same treatment as those from the Title.

The myriad potential foundational causes from the Visual Inspection component and the Streamlined component were combined.

SDM-2A5 - Validation of Potential Foundational Causes

There were 9427 potential foundational causes that resulted from combination of the above sources. Each of these terms had to be validated before inclusion in the final AD potential foundational causes taxonomy. The validation process was as follows.

The Thomson Medline search engine was the main vehicle used for validation, although in some cases Thomson Science Citation Index Expanded (SCI) had to be used, and in a very few cases, Pubmed was used. A query consisting of two components was entered into the search engine. The first component covered the core AD literature: Alzheimer* OR dementia in Title or MeSH. The second component was the potential foundational cause to be validated (e.g., smoking). The two components were intersected (e.g., (alzheimer* OR dementia) AND smoking), and some/all of the records retrieved were read. The evidence for linkages between the potential foundational cause and Alzheimer's Disease directly or surrogate endpoints was evaluated critically. This was a difficult process, compounded by the fact that adverse effects of toxic stimuli may be under-reported/mis-reported (Kostoff, 2016).

Because of the presence of duplicate terms and concepts, not all the 9427 potential foundational cause terms had to be read with the same level of certainty. Many could be eliminated by inspection, as long as the duplication was perceived.

SDM-2A - Appendix 1 - Alzheimer's Disease Causes Query - Visual Inspection Approach

1. **Core Literature Retrieval Thomson Medline** (76,663 records retrieved - core only)

TOPIC

Alzheimer*

OR

MESH HEADING

Alzheimer Disease

NOT

TOPIC

(streptozotocin OR scopolamine OR colchicine OR LPS-induc* OR polymorphism* OR abeta-induc* OR "beta-amyloid-induc*" OR "amyloid-beta-induc*" OR "beta-amyloid peptide-induc*" OR "abeta25-35-induc*" OR "abeta25-35 peptide-induc*" OR abeta40-induc* OR nontoxic OR non-toxic)

AND

Remainder of Query Intersected with Core Literature

2. TEXT FIELD TERMS

2A. NON-LIFESTYLE-SPECIFIC COMPONENT - TOPIC

("2,4,6- triiodobenzoic acid" OR "3-deazaneplanocin A" OR "5AZA" OR "5-aza-deoxycytidine" OR "5-fluorouracil" OR "9-alpha fluorocortisol" OR "9-alpha fluoroprednisolone" OR "9-hydroxy-2-methylellipticinium" OR "acarbose" OR "ACE inhibitor*" OR "acetaminophen" OR "acetazolamide" OR "acetylsalicylic acid" OR "acyclovir" OR "adalimumab" OR "adefovir" OR "adriamycin" OR "alclofenac" OR "aliskiren" OR "alizapride" OR "allopurinol" OR "all-trans-retinoic acid" OR "alpha-mercaptopropionylglycine" OR "amikacin" OR "Aminoglycoside*" OR "Amiodarone" OR "amitriptyline" OR "amlodipine" OR "amoxicillin" OR "amphetamine*" OR "amphotericin b" OR "ampicillin" OR "ampiroxicam" OR "anabolic steroid*" OR "Anaesthetic*" OR "Analgesic*" OR "anasthesia" OR "androgen deprivation therapy" OR "anesthetic*" OR "anthracycline" OR "antiadrenergic agent*" OR "anti-adrenergic agent*" OR "antiadrenergic drug*" OR "anti-adrenergic drug*" OR "antiallergic agent*" OR "Anti-Allergic agent*" OR "antiallergic drug*" OR "Anti-Allergic drug*" OR "antiandrogen* agent*" OR "anti-androgen* agent*" OR "antiandrogen* drug*" OR "anti-androgen* drug*" OR "antianginal agent*" OR "anti-anginal agent*" OR "antianginal drug*" OR "anti-anginal drug*" OR "antiangiogenesis agent*" OR "anti-angiogenesis agent*" OR "antiangiogenesis drug*" OR "anti-angiogenesis drug*" OR "antiarrhythmic agent*" OR "antiarrhythmic drug*" OR "anti-arrythmatic agent*" OR "anti-arrythmatic drug*" OR "antiasthmatic agent*" OR "anti-asthmatic agent*" OR "antiasthmatic drug*" OR "anti-asthmatic drug*" OR "antibacterial agent*" OR "Anti-bacterial agent*" OR "antibacterial drug*" OR "Anti-bacterial drug*" OR "antibiotic*" OR "antibone-loss agent*" OR "Anti-Bone-Loss agent*" OR "antibone-loss drug*" OR "Anti-Bone-Loss drug*" OR "anticholinergic agent*" OR "anti-cholinergic agent*" OR "anti-cholinergic drug*" OR "anticholinergic* drug*" OR "anticoagulant*" OR "Anti-coagulant*" OR "anticonvulsant*" OR "anti-convulsant*" OR "antidepressant*" OR "anti-depressant*"

OR "Antidiabetic agent*" OR "anti-diabetic agent*" OR "Antidiabetic drug*" OR "anti-diabetic drug*" OR "antidiarrheal agent*" OR "anti-diarrheal agent*" OR "antidiarrheal drug*" OR "anti-diarrheal drug*" OR "anti-emetic" OR "antiemetic*" OR "antifungal agent*" OR "anti-fungal agent*" OR "antifungal drug*" OR "anti-fungal drug*" OR "antigonadotropic agent*" OR "anti-gonadotropic agent*" OR "antigonadotropic drug*" OR "anti-gonadotropic drug*" OR "antigout agent*" OR "anti-gout agent*" OR "antigout drug*" OR "anti-gout drug*" OR "antihistamine agent*" OR "anti-histamine agent*" OR "antihistamine drug*" OR "anti-histamine drug*" OR "Antihypertensive agent*" OR "anti-hypertensive agent*" OR "Antihypertensive drug*" OR "anti-hypertensive drug*" OR "antiinfective agent*" OR "Anti-Infective agent*" OR "antiinfective drug*" OR "Anti-Infective drug*" OR "anti-infective*" OR "antiinflammatory agent*" OR "Anti-Inflammatory agent*" OR "antiinflammatory drug*" OR "Anti-Inflammatory drug*" OR "antimalarial agent*" OR "anti-malarial agent*" OR "antimalarial drug*" OR "anti-malarial drug*" OR "antimetabolite agent*" OR "anti-metabolite agent*" OR "antimetabolite drug*" OR "anti-metabolite drug*" OR "antimigraine agent*" OR "anti-migraine agent*" OR "antimigraine drug*" OR "anti-migraine drug*" OR "Antineoplastic Agent*" OR "anti-neoplastic agent*" OR "Antineoplastic drug*" OR "anti-neoplastic drug*" OR "antiparkinson agent*" OR "anti-parkinson agent*" OR "antiparkinson drug*" OR "anti-parkinson drug*" OR "antiplatelet agent*" OR "anti-platelet agent*" OR "antiplatelet drug*" OR "anti-platelet drug*" OR "antipseudomonal agent*" OR "anti-pseudomonal agent*" OR "antipseudomonal drug*" OR "anti-pseudomonal drug*" OR "antipsoriatic agent*" OR "anti-psoriatic agent*" OR "antipsoriatic drug*" OR "anti-psoriatic drug*" OR "Antipsychotic Agent*" OR "Anti-psychotic agent*" OR "Antipsychotic drug*" OR "Anti-psychotic drug*" OR "Antiretroviral Agent*" OR "Anti-retroviral Agent*" OR "Antiretroviral drug*" OR "Antiretroviral drug*" OR "antiretroviral therapy" OR "Antirheumatic Agent*" OR "anti-rheumatic agent*" OR "Antirheumatic drug*" OR "anti-rheumatic drug*" OR "antiseptic agent*" OR "anti-septic agent*" OR "antiseptic drug*" OR "anti-septic drug*" OR "antispasmodic agent*" OR "anti-spasmodic agent*" OR "antispasmodic drug*" OR "anti-spasmodic drug*" OR "anti-thymocyte serum" OR "Antithyroid Agent*" OR "Anti-thyroid Agent*" OR "Antithyroid drug*" OR "Anti-thyroid drug*" OR "antitoxin*" OR "anti-toxin*" OR "antituberculosis agent*" OR "anti-tuberculosis agent*" OR "antituberculosis drug*" OR "anti-tuberculosis drug*" OR "antitussive agent*" OR "anti-tussive agent*" OR "antitussive drug*" OR "anti-tussive drug*" OR "antivenin*" OR "antivertigo agent*" OR "anti-vertigo agent*" OR "antivertigo drug*" OR "anti-vertigo drug*" OR "Antiviral agent*" OR "Anti-viral agent*" OR "Antiviral drug*" OR "Anti-viral drug*" OR "aprotinin" OR "aspirin" OR "AT1 receptor antagonists" OR "atazanavir" OR "atorvastatin" OR "axitinib" OR "azacitadine" OR "azathioprine" OR "azithromycin" OR "Azole*" OR "Barbiturate*" OR "bardoxolone methyl" OR "benfluorex" OR "benoxaprofen" OR "beta-lactam" OR "bevacizumab" OR "bezafibrate" OR "bisacodyl" OR "Bisphosphonate*" OR "Bleomycin" OR "bortezomib" OR "bucillamine" OR "bupivacaine" OR "buspirone" OR "caffeine" OR "calcineurin inhibitor*" OR "calcitriol" OR "Calcium Channel Blocker" OR "Calcium channel blocker*" OR "capecitabine" OR "captopril" OR "carbamazepine" OR "carbenoxolone" OR "carbimazole" OR "carboplatin" OR "Cardiovascular Agent*" OR "carmustine" OR "C-arylsuccinimides" OR "cediranib" OR "cefdinir" OR "cefoxitin" OR "ceftriaxone" OR "cefuroxime" OR "celecoxib" OR "Central Nervous System Agent*" OR "cephaloridine" OR "cephalosporins" OR "Cephems" OR "cetuximab" OR "chlorambucil" OR "Chloramphenicol" OR "chlormezanone" OR "chloroquine" OR "Chlorpromazine" OR "chlorprothixene" OR "chlorthalidone" OR "cidofovir" OR "cimetidine" OR "ciprofibrate" OR "ciprofloxacin" OR "cisplatin" OR "clarithromycin" OR "clometacin" OR "clomipramine" OR "clopentixol" OR "clopidogrel" OR "cloxacillin" OR "clozapine" OR "colchicine" OR

"colistin" OR "contrast medium" OR "coronary artery bypass" OR "corosolic acid" OR "Corticosteroid*" OR "cyclophosphamide" OR "cycloserine" OR "cyclosporine" OR "cytarabine" OR "cytosine arabinoside" OR "dasatinib" OR "daunomycin" OR "daunorubicin" OR "decitabine" OR "deferasirox" OR "deferoxamine" OR "demeclocycline" OR "deoxycorticosterone acetate" OR "desipramine" OR "dexamethasone" OR "dexfenfluramine" OR "dexmethylphenidate" OR "dextran" OR "diaziquone" OR "diclofenac" OR "didecyldimethylammonium chloride" OR "diethyacetylurea" OR "diflunisal" OR "Digitalis" OR "diltiazem" OR "diphenylhydantoin" OR "diphosphonates" OR "dipivalyl adrenaline hydrochloride" OR "dipyrone" OR "disopyramide" OR "Diuretic*" OR "doxepin" OR "doxorubicin" OR "doxycycline" OR "d-penicillamine" OR "dRK6" OR "efavirenz" OR "enoxaparin" OR "epoetin" OR "erythromycin" OR "erythropoietin" OR "esomeprazole" OR "etanercept" OR "ethambutol" OR "ethosuximide" OR "famotidine" OR "fenbufen" OR "fenclofenac" OR "fenfluramine" OR "fenofibrate" OR "fenoldopam" OR "fenoprofen" OR "Fibrate therapy" OR "flubiprofen" OR "flucloxacillin" OR "fluindione" OR "Fluoroquinolones" OR "flupenthixol" OR "fluphenazine" OR "flurbiprofen" OR "flurithromycin" OR "fondaparinux sodium" OR "foscarnet" OR "furantoin" OR "furosemide" OR "fusidic acid" OR "FYX-051" OR "gabapentin" OR "gadodiamide" OR "Gadolinium" OR "gadopentetate dimeglumine" OR "Gastrointestinal Agent*" OR "gatifloxacin" OR "GBCA" OR "GCCA" OR "gefitinib" OR "gemcitabine" OR "gemfibrozil" OR "gentamicin" OR "germicide*" OR "Glucocorticoid*" OR "glycyrrhizinic acid" OR "Haloperidol" OR "Halothane" OR "Hematologic Agent*" OR "heparin" OR "hetastarch" OR "high insulin" OR "hydralazine" OR "hydrochlorothiazide" OR "hydroxychloroquine" OR "hydroxyethylstarch" OR "hydroxymethylglutaryl-CoA reductase inhibitor*" OR "hylan G-F 20" OR "Hypnotic Agent*" OR "iatrogenic" OR "ibuprofen" OR "ifosfamide" OR "IGF-1" OR "iloprost" OR "imatinib" OR "imipramine" OR "imiquimod" OR "Immunosuppressive Agent*" OR "indinavir" OR "indomethacin" OR "infliximab" OR "Interferon*" OR "intravenous immunoglobulin*" OR "Iodine" OR "iodixanol" OR "iohexol" OR "ionizing radiation" OR "iopamidol" OR "ioxilan" OR "iron sucrose" OR "iron-induced" OR "iron-overload" OR "isocarboxazid" OR "isoniazid" OR "isoprenaline" OR "ketamine" OR "Ketoconazole" OR "ketoprofen" OR "ketorolac" OR "lansoprazole" OR "lapatinib" OR "leflunomide" OR "levetiracetam" OR "levofloxacin" OR "Lipid Regulating Agent*" OR "lithium" OR "lopinavir" OR "loratadine" OR "loxapine" OR "mannitol" OR "maprotiline" OR "mefanamic acid" OR "meropenem" OR "mesalamine" OR "mesalazine" OR "mesoridazine" OR "metamizole" OR "metformin" OR "methicillin" OR "methimazole" OR "methocarbamol" OR "methotrexate" OR "methotrimeprazine" OR "methoxyflurance" OR "methyldopa" OR "methylphenidate" OR "methysergide" OR "metolazone" OR "metoprolol" OR "Metronidazole" OR "midecamycin acetate" OR "Mineralcorticoid*" OR "minocycline" OR "mirtazapine" OR "mitomycin" OR "Mood Stabilizer*" OR "morphine" OR "Movement Stabilizer*" OR "moxifloxacin" OR "Muscle Relaxant*" OR "Mustard gas" OR "muzolimine" OR "nafcillin" OR "naphazoline hydrochloride" OR "naproxen" OR "N-arylsuccinimides" OR "Nasal decongestant*" OR "nelfinavir" OR "neomycin" OR "Niacin" OR "nifedipine" OR "niflumic acid" OR "nimesulide" OR "nitrendipine" OR "nitrofurantoin" OR "nitrogen mustard" OR "Nitroglycerin" OR "nitrosureas" OR "nomifensine" OR "Nonsteroidal anti-inflammatory drug*" OR "norepinephrine" OR "norfloxacin" OR "nortriptyline" OR "NSAID*" OR "NVP-BKM120" OR "ofloxasin" OR "olanzapine" OR "olmetin" OR "olsalazine" OR "omeprazole" OR "orlistat" OR "oxaliplatin" OR "oxymetazoline hydrochloride" OR "oxytetracycline" OR "ozurdex" OR "paliperidone" OR "pamidronate" OR "panitumumab" OR "pantoprazole" OR "papaverine" OR "paracetamol" OR "paroxetine" OR "pazopanib" OR "pefloxacin" OR "Penams" OR "penicillamine" OR "penicillin" OR "pentamidine" OR "pentazocine" OR "pericyazine" OR

"perphenazine" OR "phenacetin" OR "phenindione" OR "phenobarbital" OR "phenylbutazone" OR "phenylephrine" OR "phenylpropanolamine" OR "phenytoin" OR "phosphatidylinositol-3-kinase inhibitor*" OR "physostigmine" OR "pimozide" OR "piperacillin" OR "piroxicam" OR "pirprofen" OR "platalet aggregation inhibitor*" OR "polymyxin B" OR "pranlukast" OR "prednisolone" OR "Primaquine" OR "probenecid" OR "procainamide" OR "prochlorperazine" OR "propoxyphene" OR "propylthiouracil" OR "protamine" OR "Proton pump inhibitor*" OR "prulifloxacin" OR "pseudoephedrine hydrochloride" OR "ptu-induced" OR "puromycin" OR "quetiapine" OR "quinacrine" OR "quinidine" OR "quinine" OR "quinolone" OR "rabeprazole" OR "radiofrequency-induced cosmetic volume reduction" OR "ranitidine" OR "rapamycin" OR "rhuepo-induced" OR "rifampicin" OR "rifampin" OR "risperidone" OR "Ritalin" OR "ritodrine hydrochloride" OR "ritonavir" OR "rofecoxib" OR "rosuvastatin" OR "scopolamine" OR "selegiline" OR "sibutramine" OR "simvastatin" OR "sodium barbital" OR "sodium valproate" OR "sorafenib" OR "spirapril" OR "spironolactone" OR "Statin*" OR "Steroid*" OR "Stimulant*" OR "streptomycin" OR "streptozocin" OR "streptozotocin" OR "Succinimide derivative*" OR "sulfadiazine" OR "sulfamethoxazole" OR "sulfasalazine" OR "Sulfonamide*" OR "sulfonylureas" OR "sulfur mustard" OR "sulindac" OR "sulphinpyrazone" OR "sulpiride" OR "sunitinib" OR "superdrol" OR "tacrolimus" OR "Tamoxifen" OR "tazobactam" OR "telazol" OR "telithromycin" OR "tenofovir" OR "testosterone" OR "tetrabenazine" OR "Tetracycline*" OR "tetrahydrozoline hydrochloride" OR "tetrandrine" OR "thiazides" OR "thiopropazate" OR "thioproperazine" OR "Thioridazine" OR "thiothixene" OR "thrombolytic therapy" OR "ticlopidine" OR "tiletamine" OR "tiopronin" OR "tobramicin" OR "triamterene" OR "trichostatin A" OR "Tricyclics" OR "trimethadione" OR "trimethoprim" OR "trimipramine" OR "tripelennamine" OR "valdecoxib" OR "Valproic Acid" OR "valpromide" OR "vancomycin" OR "venlafaxine" OR "verapamil" OR "verteporfin" OR "warfarin" OR "whole-body irradiation" OR "wortmannin" OR "yohimbine" OR "zoledronate" OR "zopiclone" OR "zotepine" OR "zuclopenthixol" OR "4-HNE" OR "7-Ketocholesterol" OR "aflatoxin" OR "Aipysurus laevis venom" OR "amorimia exotropica" OR "anti-mouse-GBM sera" OR "AOPP-modified rat serum albumin" OR "apoferritin" OR "bee sting*" OR "beta-conglycinin" OR "bovine serum albumin" OR "cantharidin" OR "ceramide" OR "citrinin" OR "concanavalin A" OR "connective tissue growth factor" OR "cow milk processing" OR "CTGF" OR "cylindrospermopsin" OR "deoxynivalenol" OR "D-fructofuranosyl" OR "Endotoxin*" OR "Exotoxin*" OR "fumonisin B1" OR "homopolysaccharide" OR "indican" OR "indoxyl sulfate" OR "levan" OR "lipopolysaccharide" OR "lipopolysaccharide-induced" OR "L-NAME" OR "L-NNA" OR "lps-induced" OR "monocrotaline" OR "monosodium urate crystal" OR "mycobacterial infection*" OR "Mycotoxin*" OR "nephritogenoside" OR "NG-nitro-L-arginine methyl ester" OR "Nitroarginine" OR "nivalenol" OR "Nω-nitro-L-arginine" OR "oak toxicosis" OR "ochratoxin A" OR "Ochratoxin*" OR "O-glycosylated IgA rheumatoid factor" OR "p-Cresyl sulfate" OR "PDGF-BB" OR "penicillic acid" OR "Platelet-derived growth factor-BB" OR "pufferfish tetrodotoxin" OR "quercus calliprinos" OR "scorpion sting*" OR "sea anemone Phyllodiscus semoni" OR "sea snake venom" OR "snake bite" OR "stinging insect venom" OR "tetrodotoxin" OR "Tityus serrulatus scorpion venom" OR "Tricothecene*" OR "U1-70-kDa small nuclear ribonucleoprotein/snRPN70" OR "viper snake venom" OR "vomitoxin" OR "wasp sting*" OR "yew" OR "*Bacteri*" OR "*Chia" OR "*Ococcus" OR "*Omonas" OR "adenine" OR "Aspergillus " OR "Bartonella henselae" OR "beta-hemolysin " OR "Brucella" OR "Burkholderia pseudomallei" OR "C. difficile toxin A" OR "C. difficile toxin B" OR "Campylobacter jejuni" OR "Campylobacter jejuni" OR "Candida albicans" OR "Candida tropicalis" OR "Candidemia" OR "Capillaria hepatica" OR "Chlamydia pneumoniae" OR "Chlamydia" OR "Chlamydophila" OR "Citrobacter

rodentium" OR "Clostridium" OR "Corynebacterium diphtheriae" OR "diphtheria toxin" OR "Corynebacterium renale" OR "Dirofilaria immitis" OR "Echinococcus" OR "Ehrlichia canis" OR "Enterococcus faecalis" OR "Escherichia coli" OR "e. coli" OR "falciparum malaria" OR "malaria" OR "Fusarium graminearum" OR "Gemella haemolysans" OR "Haemophilus" OR "Helicobacter pylori" OR "Klebsiella pneumoniae" OR "leprosy" OR "Mycobacterium leprae" OR "Mycobacterium lepromatosis" OR "Leptospirosis" OR "leptospira" OR "marcescens" OR "Mycoplasma" OR "Neisseria" OR "Nematode*" OR "Parasite*" OR "Penicillium aurantiogriseum" OR "Penicillium aurantiogriseum" OR "Plasmodium brasilianum" OR "Propionibacterium acnes" OR "Proteus mirabilis" OR "Pseudomonas aeruginosa" OR "Rickettsia" OR "Rochalimaea" OR "salmonella" OR "Schistosoma haematobium" OR "Schistosoma mansoni" OR "Serratia marcescens" OR "staphylococcal infection*" OR "Staphylococcus aureus" OR "Streptococcus agalactiae" OR "Streptococcus mutans" OR "Streptococcus pyogenes" OR "streptococcal pyrogenic exotoxin B" OR "Thy-1.1 monoclonal antibody" OR "Toxocara canis" OR "Treponema" OR "Trichinella spiralis" OR "Trypanosoma brucei" OR "Tyrophagus putrescentiae" OR "Vibrio" OR "Yersinia" OR "*OBACTER" OR "*nitrophenol*" OR "*benzene" OR "*ethane" OR "*phthalate" OR "*toluene" OR "1,1,1-trichloroethane" OR "12-O-tetradecanoylphorbol-13-acetate " OR "1-methyl-4-phenylpyridinium" OR "2,3,5-triiodobenzoic acid" OR "2,3,7,8-tetrachlorodibenzo-p-dioxin" OR "2-Amino-4-(ethylthio)butyric acid) " OR "acetaldehyde" OR "acrolein" OR "Air pollutant*" OR "air pollution" OR "aldrin" OR "alloxan" OR "alpha-Naphthylisothiocyanate" OR "aluminium" OR "aluminum" OR "ammonium perchlorate" OR "anti-trinitrophenol switch variant mAbs" OR "arsenic" OR "asbestos" OR "asphalt" OR "atrazine" OR "beryllium" OR "Bis(2-ethylhexyl) phthalate" OR "bismuth" OR "bitumen" OR "bromodichloromethane" OR "bromoform" OR "cadmium" OR "carbon tetrachloride" OR "cedar dust" OR "cerium oxide nanoparticles" OR "chloroform" OR "chlorpyrifos" OR "chromic acid " OR "chromium" OR "copper sulphate " OR "copper" OR "cotton pellets" OR "cyromazine" OR "decabrom*" OR "DEHP" OR "diazinon" OR "dibromochloromethane" OR "dichloro*" OR "diesel" OR "diethylene glycol" OR "dimethylnitrosamine " OR "dinitro*" OR "dinitrochlorobenzene" OR "dioxane" OR "dioxin " OR "domestic gas" OR "ethionine " OR "ethylene dibromide " OR "ethylene glycol" OR "fiberglass" OR "fibreglass" OR "fluoro-10-methyl-1-2-benzanthracene " OR "formaldehyde" OR "gasoline" OR "germanium" OR "glycerol" OR "grain dust" OR "halomethane* " OR "hcy-induced " OR "Heavy metal*" OR "Herbicide*" OR "hexabrom*" OR "hexachloro*" OR "hgcl2" OR "homocysteine" OR "house dust mite" OR "Hydrocarbons" OR "Insecticide*" OR "isopropyl alcohol" OR "jatropha curcas phorbol ester" OR "ketones" OR "malathion" OR "maleic vinyl ether anhydride " OR "Maneb" OR "melamine" OR "menadione sodium bisulfite" OR "mercuric chloride" OR "Mercury" OR "methyl tertiary-butyl ether " OR "methylene chloride" OR "methylglyoxal" OR "multiwalled carbon nanotube*" OR "N,N’-dimethyl-4,4’-bipyridinium dichloride" OR "N,N'-diacetylbenzidine " OR "N-3-5-dichlorophenyl-succinimide" OR "nanocopper" OR "n-methyl-n 1-nitro-n-nitroso guanidine " OR "nonylphenol" OR "octylphenol" OR "oxalates" OR "oxidant-induced" OR "p-Aminophenol" OR "parachloro*" OR "paraphenylenediamine" OR "paraquat " OR "Particulates" OR "pb" OR "pentachloro*" OR "pentachlorophenol" OR "perchloroethylene" OR "perfluor*" OR "perfluoroalkyl chemicals" OR "perfluorooctane sulfonate" OR "perfluorooctanoic acid" OR "Pesticide*" OR "Phenols" OR "phenylenediamine " OR "picric acid" OR "plant growth regulator* " OR "polybrom*" OR "polychlor*" OR "polychlorinated organic compound* " OR "polyfluor*" OR "polymethyl methacrylate " OR "potassium bichromate " OR "pristane" OR "p-xylene" OR "pyrinuron" OR "pyruvaldehyde " OR "silane " OR "silica" OR "silicon dioxide" OR "single wall carbon nanotube*" OR "styrene" OR "tetrabrom*" OR "tetrachloro*" OR "tetrachloroethylene" OR

"thioacetamide " OR "titanium dioxide nanoparticles" OR "toluene" OR "trichloro*" OR "trichloroethylene" OR "trimethylpentane" OR "trinitrobenzenesulfonic acid " OR "Trinitrophenol" OR "uranium" OR "uranyl nitrate" OR "vacor" OR "wood dust" OR "wood preservatives" OR "xylene" OR "zinc phosphide" OR "sediment-associated" OR "particle-associated" OR "traffic-related" OR "work-related" OR EMF) near/20 ("poison*" OR "ecotoxologic* effect*" OR "occupation*" OR pollut* OR "*virus*" OR environmental OR "induc*" OR "damage-caus*" OR "drug*-caus*" OR "infect*-caus*" OR "chemotherapy-caus*" OR "treat*-caus*" OR "anesthesia-caus*" OR "chemical*-caus*" OR "cytokine*-caus*" OR "surg*-caus*" OR "radiation-caus*" OR "steroid-caus*" OR "mechanically-caus*" OR "promot* progression" OR "caus* accumulation" OR "caus* * accumulation" OR "progression of" OR expos* OR contamina* OR chemicals OR abuse* OR induc* OR "long-term effect*" OR "inhibit* *protection" OR dysfunction* OR aggregation OR accumulation OR "disease link* to" OR "chemical initiator*" OR "stimulat* microglia" OR "activat* microglia" OR "increas* risk*" OR "increas* the risk*" OR "adverse event*" OR "adverse reaction*" OR "adverse * event*" OR "adverse * reaction" OR "adverse effect*" OR "adverse * effect*" OR hypersensitivity OR aggravat* OR exacerbat* OR detriment* OR "caus* *toxi*" OR "increas* *toxi" OR "produc* *toxi*" OR "enhanc* *toxi*" OR "stimulat* *toxi*" OR "accelerat* *toxi*" OR "caus* degrad*" OR "increas* degrad*" OR "caus* damag*" OR "increas* damag*" OR "caus* * *toxi*" OR "increas* * *toxi" OR "produc* * *toxi*" OR "enhanc* * *toxi*" OR "stimulat* * *toxi*" OR "accelerat* * *toxi*" OR "caus* * degrad*" OR "increas* * degrad*" OR "caus* * damag*" OR "increas* * damag*" OR "*toxi* caus* by" OR "*toxi* increas* by" OR "*toxi* produc* by" OR "*toxi* enhanc* by" OR "*toxi* stimulat* by" OR "*toxi* accelerat* by" OR "damag* caus* by" OR "*damag* increas* by" OR deleterious OR deteriorat* OR trigger* OR worsen* OR harm* OR hazard* OR "side-effect*" OR dangerous OR destructive OR injurious OR unsafe OR "increas* amyloid-beta" OR "increas* beta-amyloid" OR "increas* abeta" OR "increas* senile plaque*" OR "increas* tau aggregat*" OR "increas* T-tau" OR "increas* P-tau" OR "increas*total tau" OR "increas* phospho-tau" OR "increas* tau protein*" OR "increas* hyperphosphorylated tau" OR "increas* neurofibrillary tangle*" OR "enhanc* amyloid-beta" OR "enhanc* beta-amyloid" OR "enhanc* abeta" OR "enhanc* senile plaque*" OR "enhanc* tau aggregat*" OR "enhanc* T-tau" OR "enhanc* P-tau" OR "enhanc*total tau" OR "enhanc* phospho-tau" OR "enhanc* tau protein*" OR "enhanc* hyperphosphorylated tau" OR "enhanc* neurofibrillary tangle*" OR "stimulat* amyloid-beta" OR "stimulat* beta-amyloid" OR "stimulat* abeta" OR "stimulat* senile plaque*" OR "stimulat* tau aggregat*" OR "stimulat* T-tau" OR "stimulat* P-tau" OR "stimulat*total tau" OR "stimulat* phospho-tau" OR "stimulat* tau protein*" OR "stimulat* hyperphosphorylated tau" OR "stimulat* neurofibrillary tangle*" OR "elevat* amyloid-beta" OR "elevat* beta-amyloid" OR "elevat* abeta" OR "elevat* senile plaque*" OR "elevat* tau aggregat*" OR "elevat* T-tau" OR "elevat* P-tau" OR "elevat*total tau" OR "elevat* phospho-tau" OR "elevat* tau protein*" OR "elevat* hyperphosphorylated tau" OR "elevat* neurofibrillary tangle*" OR "induc* amyloid-beta" OR "induc* beta-amyloid" OR "induc* abeta" OR "induc* senile plaque*" OR "induc* tau aggregat*" OR "induc* T-tau" OR "induc* P-tau" OR "induc*total tau" OR "induc* phospho-tau" OR "induc* tau protein*" OR "induc* hyperphosphorylated tau" OR "induc* neurofibrillary tangle*" OR "produc* amyloid-beta" OR "produc* beta-amyloid" OR "produc* abeta" OR "produc* senile plaque*" OR "produc* tau aggregat*" OR "produc* T-tau" OR "produc* P-tau" OR "produc*total tau" OR "produc* phospho-tau" OR "produc* tau protein*" OR "produc* hyperphosphorylated tau" OR "produc* neurofibrillary tangle*" OR "accelerat* amyloid-beta" OR "accelerat* beta-amyloid" OR "accelerat* abeta" OR "accelerat* senile plaque*" OR "accelerat* tau

aggregat*" OR "accelerat* T-tau" OR "accelerat* P-tau" OR "accelerat*total tau" OR "accelerat* phospho-tau" OR "accelerat* tau protein*" OR "accelerat* hyperphosphorylated tau" OR "accelerat* neurofibrillary tangle*" OR "amyloid-beta induc* by" OR "beta-amyloid induc* by" OR "abeta induc* by" OR "senile plaque* induc* by" OR "tau aggregat* induc* by" OR "T-tau induc* by" OR "P-tau induc* by" OR "total tau induc* by" OR "phospho-tau induc* by" OR "tau protein* induc* by" OR "hyperphosphorylated tau induc* by" OR "neurofibrillary tangle* induc* by" OR "amyloid-beta produc* by" OR "beta-amyloid produc* by" OR "abeta produc* by" OR "senile plaque* produc* by" OR "tau aggregat* produc* by" OR "T-tau produc* by" OR "P-tau produc* by" OR "total tau produc* by" OR "phospho-tau produc* by" OR "tau protein* produc* by" OR "hyperphosphorylated tau produc* by" OR "neurofibrillary tangle* produc* by" OR "caus* Alzheimer*" OR "caus* dementia" OR "caus* cognitive decline" OR "caus* brain* decline" OR "caus* functional decline" OR "caus* memory decline" OR "caus* cognitive deficit*" OR "caus* language deficit*" OR "caus* memory deficit*" OR "caus* plasticity deficit*" OR "caus* behavioral deficit*" OR "caus* saccade deficit*" OR "caus* learning deficit*" OR "caus* neuropsychological deficit*" OR "caus* cognitive impair*" OR "caus* vascular impair*" OR "caus* memory impair*" OR "caus* neurogenesis impair*" OR "caus* neuropsychological impair*" OR "caus* mind impair*" OR "caus* functional impair*" OR "caus* learning impair*" OR "caus* executive function impair*" OR "caus* cognitive loss*" OR "caus* neuronal loss*" OR "caus* synaptic loss*" OR "caus* memory loss*" OR "caus* loss of memory" OR "caus* hearing loss*" OR "caus* volume loss*" OR "caus* Impair* face recognition" OR "caus* Impair* reasoning" OR "caus* Impair* judgment" OR "caus* Impair* problem solving" OR "caus* inflamm*" OR "caus* oxidative stress" OR "caus* neuropathology" OR "caus* diabetes" OR "caus* hypertension" OR "caus* high cholesterol" OR "caus* hypercholesterolemia" OR "caus* obesity" OR "caus* metabolic syndrome" OR "induc* Alzheimer*" OR "induc* dementia" OR "induc* cognitive decline" OR "induc* brain* decline" OR "induc* functional decline" OR "induc* memory decline" OR "induc* cognitive deficit*" OR "induc* language deficit*" OR "induc* memory deficit*" OR "induc* plasticity deficit*" OR "induc* behavioral deficit*" OR "induc* saccade deficit*" OR "induc* learning deficit*" OR "induc* neuropsychological deficit*" OR "induc* cognitive impair*" OR "induc* vascular impair*" OR "induc* memory impair*" OR "induc* neurogenesis impair*" OR "induc* neuropsychological impair*" OR "induc* mind impair*" OR "induc* functional impair*" OR "induc* learning impair*" OR "induc* executive function impair*" OR "induc* cognitive loss*" OR "induc* neuronal loss*" OR "induc* synaptic loss*" OR "induc* memory loss*" OR "induc* loss of memory" OR "induc* hearing loss*" OR "induc* volume loss*" OR "induc* Impair* face recognition" OR "induc* Impair* reasoning" OR "induc* Impair* judgment" OR "induc* Impair* problem solving" OR "induc* inflamm*" OR "induc* oxidative stress" OR "induc* neuropathology" OR "induc* diabetes" OR "induc* hypertension" OR "induc* high cholesterol" OR "induc* hypercholesterolemia" OR "induc* obesity" OR "induc* metabolic syndrome" OR "produc* Alzheimer*" OR "produc* dementia" OR "produc* cognitive decline" OR "produc* brain* decline" OR "produc* functional decline" OR "produc* memory decline" OR "produc* cognitive deficit*" OR "produc* language deficit*" OR "produc* memory deficit*" OR "produc* plasticity deficit*" OR "produc* behavioral deficit*" OR "produc* saccade deficit*" OR "produc* learning deficit*" OR "produc* neuropsychological deficit*" OR "produc* cognitive impair*" OR "produc* vascular impair*" OR "produc* memory impair*" OR "produc* neurogenesis impair*" OR "produc* neuropsychological impair*" OR "produc* mind impair*" OR "produc* functional impair*" OR "produc* learning impair*" OR "produc* executive function impair*" OR "produc* cognitive loss*" OR "produc* neuronal loss*" OR "produc* synaptic loss*" OR "produc*

memory loss*" OR "produc* loss of memory" OR "produc* hearing loss*" OR "produc* volume loss*" OR "produc* Impair* face recognition" OR "produc* Impair* reasoning" OR "produc* Impair* judgment" OR "produc* Impair* problem solving" OR "produc* inflamm*" OR "produc* oxidative stress" OR "produc* neuropathology" OR "produc* diabetes" OR "produc* hypertension" OR "produc* high cholesterol" OR "produc* hypercholesterolemia" OR "produc* obesity" OR "produc* metabolic syndrome" OR "increas* Alzheimer*" OR "increas* dementia" OR "increas* cognitive decline" OR "increas* brain* decline" OR "increas* functional decline" OR "increas* memory decline" OR "increas* cognitive deficit*" OR "increas* language deficit*" OR "increas* memory deficit*" OR "increas* plasticity deficit*" OR "increas* behavioral deficit*" OR "increas* saccade deficit*" OR "increas* learning deficit*" OR "increas* neuropsychological deficit*" OR "increas* cognitive impair*" OR "increas* vascular impair*" OR "increas* memory impair*" OR "increas* neurogenesis impair*" OR "increas* neuropsychological impair*" OR "increas* mind impair*" OR "increas* functional impair*" OR "increas* learning impair*" OR "increas* executive function impair*" OR "increas* cognitive loss*" OR "increas* neuronal loss*" OR "increas* synaptic loss*" OR "increas* memory loss*" OR "increas* loss of memory" OR "increas* hearing loss*" OR "increas* volume loss*" OR "increas* Impair* face recognition" OR "increas* Impair* reasoning" OR "increas* Impair* judgment" OR "increas* Impair* problem solving" OR "increas* inflamm*" OR "increas* oxidative stress" OR "increas* neuropathology" OR "increas* diabetes" OR "increas* hypertension" OR "increas* high cholesterol" OR "increas* hypercholesterolemia" OR "increas* obesity" OR "increas* metabolic syndrome" OR "exacerbat* Alzheimer*" OR "exacerbat* dementia" OR "exacerbat* cognitive decline" OR "exacerbat* brain* decline" OR "exacerbat* functional decline" OR "exacerbat* memory decline" OR "exacerbat* cognitive deficit*" OR "exacerbat* language deficit*" OR "exacerbat* memory deficit*" OR "exacerbat* plasticity deficit*" OR "exacerbat* behavioral deficit*" OR "exacerbat* saccade deficit*" OR "exacerbat* learning deficit*" OR "exacerbat* neuropsychological deficit*" OR "exacerbat* cognitive impair*" OR "exacerbat* vascular impair*" OR "exacerbat* memory impair*" OR "exacerbat* neurogenesis impair*" OR "exacerbat* neuropsychological impair*" OR "exacerbat* mind impair*" OR "exacerbat* functional impair*" OR "exacerbat* learning impair*" OR "exacerbat* executive function impair*" OR "exacerbat* cognitive loss*" OR "exacerbat* neuronal loss*" OR "exacerbat* synaptic loss*" OR "exacerbat* memory loss*" OR "exacerbat* loss of memory" OR "exacerbat* hearing loss*" OR "exacerbat* volume loss*" OR "exacerbat* Impair* face recognition" OR "exacerbat* Impair* reasoning" OR "exacerbat* Impair* judgment" OR "exacerbat* Impair* problem solving" OR "exacerbat* inflamm*" OR "exacerbat* oxidative stress" OR "exacerbat* neuropathology" OR "exacerbat* diabetes" OR "exacerbat* hypertension" OR "exacerbat* high cholesterol" OR "exacerbat* hypercholesterolemia" OR "exacerbat* obesity" OR "exacerbat* metabolic syndrome" OR "trigger* Alzheimer*" OR "trigger* dementia" OR "trigger* cognitive decline" OR "trigger* brain* decline" OR "trigger* functional decline" OR "trigger* memory decline" OR "trigger* cognitive deficit*" OR "trigger* language deficit*" OR "trigger* memory deficit*" OR "trigger* plasticity deficit*" OR "trigger* behavioral deficit*" OR "trigger* saccade deficit*" OR "trigger* learning deficit*" OR "trigger* neuropsychological deficit*" OR "trigger* cognitive impair*" OR "trigger* vascular impair*" OR "trigger* memory impair*" OR "trigger* neurogenesis impair*" OR "trigger* neuropsychological impair*" OR "trigger* mind impair*" OR "trigger* functional impair*" OR "trigger* learning impair*" OR "trigger* executive function impair*" OR "trigger* cognitive loss*" OR "trigger* neuronal loss*" OR "trigger* synaptic loss*" OR "trigger* memory loss*" OR "trigger* loss of memory" OR "trigger* hearing loss*" OR "trigger* volume loss*" OR "trigger* Impair* face recognition"

OR "trigger* Impair* reasoning" OR "trigger* Impair* judgment" OR "trigger* Impair* problem solving" OR "trigger* inflamm*" OR "trigger* oxidative stress" OR "trigger* neuropathology" OR "trigger* diabetes" OR "trigger* hypertension" OR "trigger* high cholesterol" OR "trigger* hypercholesterolemia" OR "trigger* obesity" OR "trigger* metabolic syndrome" OR "accelerat* Alzheimer*" OR "accelerat* dementia" OR "accelerat* cognitive decline" OR "accelerat* brain* decline" OR "accelerat* functional decline" OR "accelerat* memory decline" OR "accelerat* cognitive deficit*" OR "accelerat* language deficit*" OR "accelerat* memory deficit*" OR "accelerat* plasticity deficit*" OR "accelerat* behavioral deficit*" OR "accelerat* saccade deficit*" OR "accelerat* learning deficit*" OR "accelerat* neuropsychological deficit*" OR "accelerat* cognitive impair*" OR "accelerat* vascular impair*" OR "accelerat* memory impair*" OR "accelerat* neurogenesis impair*" OR "accelerat* neuropsychological impair*" OR "accelerat* mind impair*" OR "accelerat* functional impair*" OR "accelerat* learning impair*" OR "accelerat* executive function impair*" OR "accelerat* cognitive loss*" OR "accelerat* neuronal loss*" OR "accelerat* synaptic loss*" OR "accelerat* memory loss*" OR "accelerat* loss of memory" OR "accelerat* hearing loss*" OR "accelerat* volume loss*" OR "accelerat* Impair* face recognition" OR "accelerat* Impair* reasoning" OR "accelerat* Impair* judgment" OR "accelerat* Impair* problem solving" OR "accelerat* inflamm*" OR "accelerat* oxidative stress" OR "accelerat* neuropathology" OR "accelerat* diabetes" OR "accelerat* hypertension" OR "accelerat* high cholesterol" OR "accelerat* hypercholesterolemia" OR "accelerat* obesity" OR "accelerat* metabolic syndrome" OR "Alzheimer* * caused by" OR "dementia caused by" OR "cognitive decline caused by" OR "brain* decline caused by" OR "functional decline caused by" OR "memory decline caused by" OR "cognitive deficit* caused by" OR "language deficit* caused by" OR "memory deficit* caused by" OR "plasticity deficit* caused by" OR "behavioral deficit* caused by" OR "saccade deficit* caused by" OR "learning deficit* caused by" OR "neuropsychological deficit* caused by" OR "cognitive impair* caused by" OR "vascular impair* caused by" OR "memory impair* caused by" OR "neurogenesis impair* caused by" OR "neuropsychological impair* caused by" OR "mind impair* caused by" OR "functional impair* caused by" OR "learning impair* caused by" OR " executive function impair* caused by" OR "cognitive loss* caused by" OR "neuronal loss* caused by" OR "synaptic loss* caused by" OR "memory loss* caused by" OR "loss of memory caused by" OR "hearing loss* caused by" OR "volume loss* caused by" OR "Impair* face recognition caused by" OR "Impair* reasoning caused by" OR "Impair* judgment caused by" OR "Impair* problem solving caused by" OR "inflamm* caused by" OR "oxidative stress caused by" OR "neuropathology caused by" OR "diabetes caused by" OR "hypertension caused by" OR "high cholesterol caused by" OR "hypercholesterolemia caused by" OR "obesity caused by" OR "metabolic syndrome caused by" OR "Alzheimer* * induced by" OR "dementia induced by" OR "cognitive decline induced by" OR "brain* decline induced by" OR "functional decline induced by" OR "memory decline induced by" OR "cognitive deficit* induced by" OR "language deficit* induced by" OR "memory deficit* induced by" OR "plasticity deficit* induced by" OR "behavioral deficit* induced by" OR "saccade deficit* induced by" OR "learning deficit* induced by" OR "neuropsychological deficit* induced by" OR "cognitive impair* induced by" OR "vascular impair* induced by" OR "memory impair* induced by" OR "neurogenesis impair* induced by" OR "neuropsychological impair* induced by" OR "mind impair* induced by" OR "functional impair* induced by" OR "learning impair* induced by" OR " executive function impair* induced by" OR "cognitive loss* induced by" OR "neuronal loss* induced by" OR "synaptic loss* induced by" OR "memory loss* induced by" OR "loss of memory induced by" OR "hearing loss* induced by" OR "volume loss* induced by" OR "Impair* face recognition induced by" OR "Impair*

reasoning induced by" OR "Impair* judgment induced by" OR "Impair* problem solving induced by" OR "inflamm* induced by" OR "oxidative stress induced by" OR "neuropathology induced by" OR "diabetes induced by" OR "hypertension induced by" OR "high cholesterol induced by" OR "hypercholesterolemia induced by" OR "obesity induced by" OR "metabolic syndrome induced by")

OR

2B. LIFESTYLE-SPECIFIC COMPONENT

2B1. LIFESTYLE-SPECIFIC COMPONENT - TOPIC

("2,3-Pentanedione" OR "acidogenic diet*" OR "acrylamide" OR "activity restriction" OR "acute stress" OR "additives" OR "advanced glycation end product*" OR "Advanced glycosylation end product*" OR "adverse food" OR "alcohol abuse*" OR "alcohol consum*" OR "alcohol intake" OR "alcoholic*" OR "alcohol-induc*" OR "alcoholism" OR "Amanita phalloides" OR "amphetamine*" OR "anabolic steroid*" OR "areca nut chewing" OR arnica OR "aspartame" OR "betel nut chewing" OR "binge eating" OR "biomass fuel for cooking" OR "bitter orange" OR "caffeine" OR "childhood adversity" OR "chinese herb*" OR "chlorogenic acid" OR "cholesterol-induced" OR "cigarette*" OR "cocaine" OR "cola" OR "competitive strength exercise training" OR cortinarius OR "dehydration" OR "depression-caus*" OR "depression-induc*" OR dextrose OR diet* near/1 effect* OR diet*-caus* OR diet*-induc* OR dietborne OR "djenkol beans" OR "early-life abuse" OR "eating fast" OR "effort-reward imbalance" OR "emotional abuse" OR ephedra OR "exercise-caus*" OR "folic acid-induc*" OR "food additive" OR "food poisoning" OR "free-fatty-acid-induced" OR "fructose" OR "germ-free" OR "glucose-induc*" OR "glucose-peaks-short-term" OR "gluten" OR glycerin OR guarana OR "heat stroke" OR "heroin" OR "high home temperature" OR "high insulin" OR "high meat" OR "high selenium diet" OR "high-fat-diet*" OR "high-glucose-induc*" OR "High-glycemic-load diet*" OR "high-phosphate" OR "high-phosphorous-diet*" OR "high-protein-diet*" OR "high-protein-induc*" OR "high-protein-intake*" OR "high-salt-diet*" OR "high-salt-intake*" OR "high-saturated-fat diet*" OR "high-sodium-diet*" OR "high-sodium-intake*" OR "high-soybean oil" OR "high-sucrose-diet*" OR "high-sugar-diet*" OR "high-tryptophan-diet*" OR "Highway proximity" OR hypothermia OR "hypoxia-induced" OR "insufficient sleep" OR "job strain" OR "laxative abuse" OR "low fiber diet*" OR "low fiber intake" OR "low legumes intake" OR "low manganese intake" OR "low melatonin" OR "low potassium intake" OR "low pulses intake" OR "low-Vitamin D intake" OR "meat" OR "milk processing" OR "morphine" OR mothball* OR "mushrooms" OR noise OR "overfeeding" OR palmitate OR "palmitic acid" OR "parental hypertension" OR "parental occupation*" OR "parental sucrose" OR "persistent organic pollutants" OR "phosphorus additive*" OR "physical inactivity" OR "prenatal hypoxia" OR "preserved food*" OR "preserved meat*" OR "prolonged sitting" OR "psychogenic polydipsia" OR "psychological trauma" OR "refined carbohydrate*" OR "refined cereal*" OR "refined grain*" OR "refined flour" OR "residential remoteness" OR "salt-induced" OR "saturated fat*" OR "sedentary" OR "short sleep duration" OR "sitting time" OR "sleep deprivation" OR "smoking" OR "social environment" OR "sodium additive*" OR "soft drink*" OR "soybean oil heated repeatedly" OR "soy-rich diet" OR "star fruit" OR "sucralose" OR "sunflower oil" OR "tobacco" OR "trans-fat*" OR "water-borne" OR "zinc-deficient diet" OR low near/2 sunlight OR waterborne)

OR

2B2. LIFESTYLE-SPECIFIC COMPONENT - TITLE

(diet* near/1 effect* OR "adverse food" OR "additives" OR exercise-induc* OR diet*-induc* OR exercise-caus* OR diet*-caus* OR waterborne OR "water-borne" OR dietborne OR "acidogenic diet*" OR "activity restriction" OR "advanced glycation end product*" OR "Advanced glycosylation end product*" OR "alcohol abuse*" OR "alcohol consum*" OR "alcohol intake" OR "alcoholic*" OR "alcohol-induc*" OR "alcoholism" OR "amphetamine*" OR "anabolic steroid*" OR "areca nut chewing" OR "betel nut chewing" OR "binge eating" OR "caffeine" OR "childhood adversity" OR "chinese herb*" OR "cholesterol-induced" OR "cigarette*" OR "cocaine" OR "cola" OR "milk processing" OR "dehydration" OR "depression-induc*" OR "depression-caus*" OR "effort-reward imbalance" OR "emotional abuse" OR "Exercise-induced" OR "folic acid-induc*" OR "free-fatty-acid-induced" OR "fructose" OR "germ-free" OR "glucose-induc*" OR "glucose-peaks-short-term" OR "gluten" OR "heat stroke" OR "heroin" OR "high-fat-diet*" OR "high-glucose-induc*" OR "High-glycemic-load diet*" OR "high home temperature" OR "high insulin" OR "high meat" OR "high-phosphate" OR "high-phosphorous-diet*" OR "high-protein-diet*" OR "high-protein-intake*" OR "high-protein-induc*" OR "high-salt-diet*" OR "high-salt-intake*" OR "high-saturated-fat diet*" OR "high selenium diet" OR "high-sodium-intake*" OR "high-sodium-diet*" OR "high-soybean oil" OR "high-sucrose-diet*" OR "high-tryptophan-diet*" OR "job strain" OR "laxative abuse" OR "psychological trauma" OR "competitive strength exercise training" OR "low fiber diet*" OR "low fiber intake" OR "low legumes intake" OR "low manganese intake" OR "low melatonin" OR "low potassium intake" OR "low pulses intake" OR "low-Vitamin D intake" OR "meat" OR "morphine" OR "mothball abuse" OR "mushrooms" OR "parental sucrose" OR "phosphorus additive*" OR "physical inactivity" OR "refined cereal*" OR "residential remoteness" OR "salt-induced" OR "sedentary" OR "short sleep duration" OR "sitting time" OR "sleep deprivation" OR "smoking" OR "social environment" OR "sodium additive*" OR "soybean oil heated repeatedly" OR "soy-rich diet" OR "star fruit" OR "stress-induced" OR "sunflower oil" OR "tobacco" OR "overfeeding" OR "zinc-deficient diet" OR "TRANS-FAT*" OR "2,3-Pentanedione" OR "acute stress" OR "biomass fuel for cooking" OR "early-life abuse" OR "Highway proximity" OR "parental occupation*" OR "Sugar" OR "Refined Carbohydrate*" OR "Acrylamide" OR "Aspartame" OR "Sucralose" OR "Preserved Meat*" OR "Refined Flour" OR "Saturated Fat*" OR "Soft Drink*" OR "Preserved Food*" OR "Insufficient Sleep")

OR

3. MESH FIELD TERMS

RUN 3A1 AND 3B1 AS ONE QUERY

3A. MESH QUALIFIERS - MESH HEADING

3A1. NON-LIFESTYLE-SPECIFIC COMPONENT

(/"chemically induced" OR /toxicity OR /poisoning)

OR

3B. MESH GENERIC TERMS - MESH HEADING NO EXPLODE

3B1. NON-LIFESTYLE-SPECIFIC COMPONENT - MESH HEADING NO EXPLODE

Abnormalities, Drug-Induced OR Aids Related Opportunistic Infections OR Air Pollutants, Occupational OR Bacterial Infections OR Congenital Abnormalities OR Congenital Disorders Of Glycosylation OR Dermatitis, Occupational OR Drug Eruptions OR Drug Hypersensitivity OR Drug Toxicity OR Environmental Exposure OR Environmental Illness OR Environmental Monitoring OR Environmental Pollutants OR Fossil Fuels OR Hazardous Substances OR Herbicides OR Household Products OR HTLV I Infections OR Iatrogenic Disease OR Inhalation Exposure OR Insecticides OR Marine Toxins OR Maternal Exposure OR Mutagens OR Mycotoxins OR Neurotoxins OR Nonprescription Drugs OR Occupational Diseases OR Occupational Exposure OR Occupations OR Opportunistic Infections OR Organic Chemicals OR Paternal Exposure OR Pesticides OR Plant Poisoning OR Plants, Toxic OR Poisoning OR Poisons OR Prenatal Exposure Delayed Effects OR Simplexvirus OR Soil Pollutants OR Solvents OR Streptococcal Infections OR Vehicle Emissions OR Water Pollutants, Chemical OR Welding

OR

3B2. LIFESTYLE-SPECIFIC COMPONENT - MESH HEADING NO EXPLODE

Alcohol Drinking OR Alcoholic Intoxication OR Alcoholism OR Alcohol-Related Disorders OR Amphetamine-Related Disorders OR Amphetamines OR Appetite Depressants OR Carbonated Beverages OR Cocaine OR Cocaine-Related Disorders OR Cola OR Contraceptive Agents OR Contraceptives, Oral OR Cooking And Eating Utensils OR Cosmetics OR Diet, High-Fat OR Fast Foods OR Food Additives OR Food Contamination OR Food Habits OR Food Preservatives OR Fructose OR Glycemic Index OR Glycosylation End Products, Advanced/adverse effects OR Hair Dyes OR Hallucinogens OR Hazardous Substances OR Heat Stroke OR Heroin OR Heroin Dependence OR Laxatives OR Leisure Activities OR Marijuana Abuse OR Methadone OR Mushroom Poisoning OR Narcotics OR Nonprescription Drugs OR Plant Poisoning OR Plants, Toxic OR Prenatal Exposure Delayed Effects OR Smoking OR Sodium Chloride, Dietary OR Sodium, Dietary OR Street Drugs OR Substance-Related Disorders OR Sweetening Agents OR Tattooing OR Tobacco OR Tobacco Smoke Pollution OR Tobacco Use Disorder OR Substance Withdrawal Syndrome OR Obesity OR Meat OR Foodborne Diseases OR Food Handling OR Dietary Fats OR Dietary Carbohydrates OR Plants Genetically Modified OR Sucrose OR Behavior Addictive OR Meat Products OR Poverty OR Maternal Exposure OR Flavoring Agents OR Diet High Fat OR Coffee OR Dairy Products OR Nutrition Disorders OR Prenatal Care OR Child Abuse OR Television OR Hygiene OR Doping In Sports OR Maternal Behavior OR Dietary Sucrose OR Thiamine Deficiency OR Folic Acid Deficiency OR Vitamin D Deficiency OR Cholesterol Dietary OR Lifestyle OR Sedentary Lifestyle OR Eating Disorders OR Sleep Disorders OR Paternal Exposure

OR

MESH TERMS DRUGS

3B3a. TITLE

("poison*" OR "ecotoxologic* effect*" OR "occupation*" OR pollut* OR "*virus*" OR environmental OR "induc*" OR "damage-caus*" OR "drug*-caus*" OR "infect*-caus*" OR "chemotherapy-caus*" OR "treat*-caus*" OR "anesthesia-caus*" OR "chemical*-caus*" OR "cytokine*-caus*" OR "surg*-caus*" OR "radiation-caus*" OR "steroid-caus*" OR "mechanically-caus*" OR "promot* progression" OR "caus* accumulation" OR "caus* * accumulation" OR "progression of" OR expos* OR contamina* OR abuse* OR

induc* OR "long-term effect*" OR "inhibit* *protection" OR dysfunction* OR aggregation OR accumulation OR "disease link* to" OR "chemical initiator*" OR "stimulat* microglia" OR "activat* microglia" OR "increas* risk*" OR "increas* the risk*" OR "adverse event*" OR "adverse reaction*" OR "adverse * event*" OR "adverse * reaction" OR "adverse effect*" OR "adverse * effect*" OR hypersensitivity OR aggravat* OR exacerbat* OR detriment* OR "caus* *toxi*" OR "increas* *toxi" OR "produc* *toxi*" OR "enhanc* *toxi*" OR "stimulat* *toxi*" OR "accelerat* *toxi*" OR "caus* degrad*" OR "increas* degrad*" OR "caus* damag*" OR "increas* damag*" OR "caus* * *toxi*" OR "increas* * *toxi" OR "produc* * *toxi*" OR "enhanc* * *toxi*" OR "stimulat* * *toxi*" OR "accelerat* * *toxi*" OR "caus* * degrad*" OR "increas* * degrad*" OR "caus* * damag*" OR "increas* * damag*" OR "*toxi* caus* by" OR "*toxi* increas* by" OR "*toxi* produc* by" OR "*toxi* enhanc* by" OR "*toxi* stimulat* by" OR "*toxi* accelerat* by" OR "damag* caus* by" OR "*damag* increas* by" OR deleterious OR deteriorat* OR trigger* OR worsen* OR harm* OR hazard* OR "side-effect*" OR dangerous OR destructive OR injurious OR unsafe)

AND

MESH HEADING NO EXPLODE

Antineoplastic Agents OR Anticoagulants OR Antineoplastic Combined Chemotherapy Protocols OR Anti-Inflammatory Agents, Non-Steroidal OR Hypoglycemic Agents OR Anti-Bacterial Agents OR Antipsychotic Agents OR Immunosuppressive Agents OR Anticonvulsants OR Platelet Aggregation Inhibitors OR Glucocorticoids OR Analgesics, Opioid OR Drug-Related Side Effects and Adverse Reactions OR Warfarin OR Analgesics OR Doxorubicin OR Cisplatin OR Protein Kinase Inhibitors OR Fibrinolytic Agents OR Fluorouracil OR Antirheumatic Agents OR Antihypertensive Agents OR Pyridines OR Cyclophosphamide OR Bone Density Conservation Agents OR Antiviral Agents OR Bleomycin OR Antidepressive Agents OR Serotonin Uptake Inhibitors OR Thiophenes OR Antibiotics, Antineoplastic OR Angiogenesis Inhibitors OR Drug Hypersensitivity OR Proton Pump Inhibitors OR Deoxycytidine OR Ticlopidine OR Organoplatinum Compounds OR Anti-Arrhythmia Agents OR Angiotensin-Converting Enzyme Inhibitors OR Anti-HIV Agents OR Paclitaxel OR Chemotherapy, Adjuvant OR Acetaminophen OR Quinazolines OR Taxoids OR Vasodilator Agents OR Pilocarpine OR Triazoles OR Benzodiazepines OR Anti-Infective Agents OR Estrogens OR Thiazolidinediones OR Antineoplastic Agents, Hormonal OR Antineoplastic Agents, Phytogenic OR Cyclooxygenase 2 Inhibitors OR Anti-Ulcer Agents OR Cyclosporine OR Vasoconstrictor Agents OR Anthracyclines OR Anticarcinogenic Agents OR Convulsants OR Calcium Channel Blockers OR Cardiotonic Agents OR Dermatologic Agents OR Isoproterenol OR Antifungal Agents OR Ribavirin OR Antiparkinson Agents OR Clozapine OR Carboplatin OR Tamoxifen OR Antiretroviral Therapy, Highly Active OR Vincristine OR Cholinesterase Inhibitors OR Antidepressive Agents, Second-Generation OR Antitubercular Agents OR Hypolipidemic Agents OR Antineoplastic Agents, Alkylating OR Gastrointestinal Agents OR Aromatase Inhibitors OR Antithyroid Agents OR Organophosphonates OR Cyclooxygenase Inhibitors OR Antidepressive Agents, Tricyclic OR Antimanic Agents OR Phosphodiesterase 5 Inhibitors OR Dipeptidyl-Peptidase IV Inhibitors OR Anti-Retroviral Agents OR Methyl Ethers OR Chelating Agents OR Anticholesteremic Agents OR Contraceptive Agents, Female OR Anti-Asthmatic Agents OR Dopamine Uptake Inhibitors OR HIV Protease Inhibitors OR N-Methyl-3,4-methylenedioxyamphetamine OR Mycophenolic Acid OR Bronchodilator Agents OR Hydroxychloroquine OR Neurotransmitter Agents OR Anti-Obesity Agents OR Anabolic Agents OR Anesthetics OR Cardiovascular Agents OR Histone Deacetylase Inhibitors OR Alkylating Agents OR Chloroquine OR

Antifibrinolytic Agents OR Benzoxazines OR Protease Inhibitors OR Fertility Agents, Female OR Dopamine Agents OR Anti-Infective Agents, Local OR Reverse Transcriptase Inhibitors OR Neuromuscular Agents OR Anti-Allergic Agents OR Monoamine Oxidase Inhibitors OR Neuromuscular Nondepolarizing Agents OR Nootropic Agents OR Photosensitizing Agents OR 5-alpha Reductase Inhibitors OR Sweetening Agents OR Sensory System Agents OR Adrenergic Agents OR Adrenergic Uptake Inhibitors OR Indicators and Reagents OR Antitussive Agents OR Surface-Active Agents OR Antimutagenic Agents

OR

3B3b. TOPIC

("increas* amyloid-beta" OR "increas* beta-amyloid" OR "increas* abeta" OR "increas* senile plaque*" OR "increas* tau aggregat*" OR "increas* T-tau" OR "increas* P-tau" OR "increas*total tau" OR "increas* phospho-tau" OR "increas* tau protein*" OR "increas* hyperphosphorylated tau" OR "increas* neurofibrillary tangle*" OR "enhanc* amyloid-beta" OR "enhanc* beta-amyloid" OR "enhanc* abeta" OR "enhanc* senile plaque*" OR "enhanc* tau aggregat*" OR "enhanc* T-tau" OR "enhanc* P-tau" OR "enhanc*total tau" OR "enhanc* phospho-tau" OR "enhanc* tau protein*" OR "enhanc* hyperphosphorylated tau" OR "enhanc* neurofibrillary tangle*" OR "stimulat* amyloid-beta" OR "stimulat* beta-amyloid" OR "stimulat* abeta" OR "stimulat* senile plaque*" OR "stimulat* tau aggregat*" OR "stimulat* T-tau" OR "stimulat* P-tau" OR "stimulat*total tau" OR "stimulat* phospho-tau" OR "stimulat* tau protein*" OR "stimulat* hyperphosphorylated tau" OR "stimulat* neurofibrillary tangle*" OR "elevat* amyloid-beta" OR "elevat* beta-amyloid" OR "elevat* abeta" OR "elevat* senile plaque*" OR "elevat* tau aggregat*" OR "elevat* T-tau" OR "elevat* P-tau" OR "elevat*total tau" OR "elevat* phospho-tau" OR "elevat* tau protein*" OR "elevat* hyperphosphorylated tau" OR "elevat* neurofibrillary tangle*" OR "induc* amyloid-beta" OR "induc* beta-amyloid" OR "induc* abeta" OR "induc* senile plaque*" OR "induc* tau aggregat*" OR "induc* T-tau" OR "induc* P-tau" OR "induc*total tau" OR "induc* phospho-tau" OR "induc* tau protein*" OR "induc* hyperphosphorylated tau" OR "induc* neurofibrillary tangle*" OR "produc* amyloid-beta" OR "produc* beta-amyloid" OR "produc* abeta" OR "produc* senile plaque*" OR "produc* tau aggregat*" OR "produc* T-tau" OR "produc* P-tau" OR "produc*total tau" OR "produc* phospho-tau" OR "produc* tau protein*" OR "produc* hyperphosphorylated tau" OR "produc* neurofibrillary tangle*" OR "accelerat* amyloid-beta" OR "accelerat* beta-amyloid" OR "accelerat* abeta" OR "accelerat* senile plaque*" OR "accelerat* tau aggregat*" OR "accelerat* T-tau" OR "accelerat* P-tau" OR "accelerat*total tau" OR "accelerat* phospho-tau" OR "accelerat* tau protein*" OR "accelerat* hyperphosphorylated tau" OR "accelerat* neurofibrillary tangle*" OR "amyloid-beta induc* by" OR "beta-amyloid induc* by" OR "abeta induc* by" OR "senile plaque* induc* by" OR "tau aggregat* induc* by" OR "T-tau induc* by" OR "P-tau induc* by" OR "total tau induc* by" OR "phospho-tau induc* by" OR "tau protein* induc* by" OR "hyperphosphorylated tau induc* by" OR "neurofibrillary tangle* induc* by" OR "amyloid-beta produc* by" OR "beta-amyloid produc* by" OR "abeta produc* by" OR "senile plaque* produc* by" OR "tau aggregat* produc* by" OR "T-tau produc* by" OR "P-tau produc* by" OR "total tau produc* by" OR "phospho-tau produc* by" OR "tau protein* produc* by" OR "hyperphosphorylated tau produc* by" OR "neurofibrillary tangle* produc* by" OR "caus* Alzheimer*" OR "caus* dementia" OR "caus* cognitive decline" OR "caus* brain* decline" OR "caus* functional decline" OR "caus* memory decline" OR "caus* cognitive deficit*" OR "caus* language deficit*" OR "caus* memory deficit*" OR "caus* plasticity

deficit*" OR "caus* behavioral deficit*" OR "caus* saccade deficit*" OR "caus* learning deficit*" OR "caus* neuropsychological deficit*" OR "caus* cognitive impair*" OR "caus* vascular impair*" OR "caus* memory impair*" OR "caus* neurogenesis impair*" OR "caus* neuropsychological impair*" OR "caus* mind impair*" OR "caus* functional impair*" OR "caus* learning impair*" OR "caus* executive function impair*" OR "caus* cognitive loss*" OR "caus* neuronal loss*" OR "caus* synaptic loss*" OR "caus* memory loss*" OR "caus* loss of memory" OR "caus* hearing loss*" OR "caus* volume loss*" OR "caus* Impair* face recognition" OR "caus* Impair* reasoning" OR "caus* Impair* judgment" OR "caus* Impair* problem solving" OR "caus* inflamm*" OR "caus* oxidative stress" OR "caus* neuropathology" OR "caus* diabetes" OR "caus* hypertension" OR "caus* high cholesterol" OR "caus* hypercholesterolemia" OR "caus* obesity" OR "caus* metabolic syndrome" OR "induc* Alzheimer*" OR "induc* dementia" OR "induc* cognitive decline" OR "induc* brain* decline" OR "induc* functional decline" OR "induc* memory decline" OR "induc* cognitive deficit*" OR "induc* language deficit*" OR "induc* memory deficit*" OR "induc* plasticity deficit*" OR "induc* behavioral deficit*" OR "induc* saccade deficit*" OR "induc* learning deficit*" OR "induc* neuropsychological deficit*" OR "induc* cognitive impair*" OR "induc* vascular impair*" OR "induc* memory impair*" OR "induc* neurogenesis impair*" OR "induc* neuropsychological impair*" OR "induc* mind impair*" OR "induc* functional impair*" OR "induc* learning impair*" OR "induc* executive function impair*" OR "induc* cognitive loss*" OR "induc* neuronal loss*" OR "induc* synaptic loss*" OR "induc* memory loss*" OR "induc* loss of memory" OR "induc* hearing loss*" OR "induc* volume loss*" OR "induc* Impair* face recognition" OR "induc* Impair* reasoning" OR "induc* Impair* judgment" OR "induc* Impair* problem solving" OR "induc* inflamm*" OR "induc* oxidative stress" OR "induc* neuropathology" OR "induc* diabetes" OR "induc* hypertension" OR "induc* high cholesterol" OR "induc* hypercholesterolemia" OR "induc* obesity" OR "induc* metabolic syndrome" OR "produc* Alzheimer*" OR "produc* dementia" OR "produc* cognitive decline" OR "produc* brain* decline" OR "produc* functional decline" OR "produc* memory decline" OR "produc* cognitive deficit*" OR "produc* language deficit*" OR "produc* memory deficit*" OR "produc* plasticity deficit*" OR "produc* behavioral deficit*" OR "produc* saccade deficit*" OR "produc* learning deficit*" OR "produc* neuropsychological deficit*" OR "produc* cognitive impair*" OR "produc* vascular impair*" OR "produc* memory impair*" OR "produc* neurogenesis impair*" OR "produc* neuropsychological impair*" OR "produc* mind impair*" OR "produc* functional impair*" OR "produc* learning impair*" OR "produc* executive function impair*" OR "produc* cognitive loss*" OR "produc* neuronal loss*" OR "produc* synaptic loss*" OR "produc* memory loss*" OR "produc* loss of memory" OR "produc* hearing loss*" OR "produc* volume loss*" OR "produc* Impair* face recognition" OR "produc* Impair* reasoning" OR "produc* Impair* judgment" OR "produc* Impair* problem solving" OR "produc* inflamm*" OR "produc* oxidative stress" OR "produc* neuropathology" OR "produc* diabetes" OR "produc* hypertension" OR "produc* high cholesterol" OR "produc* hypercholesterolemia" OR "produc* obesity" OR "produc* metabolic syndrome" OR "increas* Alzheimer*" OR "increas* dementia" OR "increas* cognitive decline" OR "increas* brain* decline" OR "increas* functional decline" OR "increas* memory decline" OR "increas* cognitive deficit*" OR "increas* language deficit*" OR "increas* memory deficit*" OR "increas* plasticity deficit*" OR "increas* behavioral deficit*" OR "increas* saccade deficit*" OR "increas* learning deficit*" OR "increas* neuropsychological deficit*" OR "increas* cognitive impair*" OR "increas* vascular impair*" OR "increas* memory impair*" OR "increas* neurogenesis impair*" OR "increas* neuropsychological impair*" OR "increas* mind impair*" OR "increas* functional impair*" OR "increas*

learning impair*" OR "increas* executive function impair*" OR "increas* cognitive loss*" OR "increas* neuronal loss*" OR "increas* synaptic loss*" OR "increas* memory loss*" OR "increas* loss of memory" OR "increas* hearing loss*" OR "increas* volume loss*" OR "increas* Impair* face recognition" OR "increas* Impair* reasoning" OR "increas* Impair* judgment" OR "increas* Impair* problem solving" OR "increas* inflamm*" OR "increas* oxidative stress" OR "increas* neuropathology" OR "increas* diabetes" OR "increas* hypertension" OR "increas* high cholesterol" OR "increas* hypercholesterolemia" OR "increas* obesity" OR "increas* metabolic syndrome" OR "exacerbat* Alzheimer*" OR "exacerbat* dementia" OR "exacerbat* cognitive decline" OR "exacerbat* brain* decline" OR "exacerbat* functional decline" OR "exacerbat* memory decline" OR "exacerbat* cognitive deficit*" OR "exacerbat* language deficit*" OR "exacerbat* memory deficit*" OR "exacerbat* plasticity deficit*" OR "exacerbat* behavioral deficit*" OR "exacerbat* saccade deficit*" OR "exacerbat* learning deficit*" OR "exacerbat* neuropsychological deficit*" OR "exacerbat* cognitive impair*" OR "exacerbat* vascular impair*" OR "exacerbat* memory impair*" OR "exacerbat* neurogenesis impair*" OR "exacerbat* neuropsychological impair*" OR "exacerbat* mind impair*" OR "exacerbat* functional impair*" OR "exacerbat* learning impair*" OR "exacerbat* executive function impair*" OR "exacerbat* cognitive loss*" OR "exacerbat* neuronal loss*" OR "exacerbat* synaptic loss*" OR "exacerbat* memory loss*" OR "exacerbat* loss of memory" OR "exacerbat* hearing loss*" OR "exacerbat* volume loss*" OR "exacerbat* Impair* face recognition" OR "exacerbat* Impair* reasoning" OR "exacerbat* Impair* judgment" OR "exacerbat* Impair* problem solving" OR "exacerbat* inflamm*" OR "exacerbat* oxidative stress" OR "exacerbat* neuropathology" OR "exacerbat* diabetes" OR "exacerbat* hypertension" OR "exacerbat* high cholesterol" OR "exacerbat* hypercholesterolemia" OR "exacerbat* obesity" OR "exacerbat* metabolic syndrome" OR "trigger* Alzheimer*" OR "trigger* dementia" OR "trigger* cognitive decline" OR "trigger* brain* decline" OR "trigger* functional decline" OR "trigger* memory decline" OR "trigger* cognitive deficit*" OR "trigger* language deficit*" OR "trigger* memory deficit*" OR "trigger* plasticity deficit*" OR "trigger* behavioral deficit*" OR "trigger* saccade deficit*" OR "trigger* learning deficit*" OR "trigger* neuropsychological deficit*" OR "trigger* cognitive impair*" OR "trigger* vascular impair*" OR "trigger* memory impair*" OR "trigger* neurogenesis impair*" OR "trigger* neuropsychological impair*" OR "trigger* mind impair*" OR "trigger* functional impair*" OR "trigger* learning impair*" OR "trigger* executive function impair*" OR "trigger* cognitive loss*" OR "trigger* neuronal loss*" OR "trigger* synaptic loss*" OR "trigger* memory loss*" OR "trigger* loss of memory" OR "trigger* hearing loss*" OR "trigger* volume loss*" OR "trigger* Impair* face recognition" OR "trigger* Impair* reasoning" OR "trigger* Impair* judgment" OR "trigger* Impair* problem solving" OR "trigger* inflamm*" OR "trigger* oxidative stress" OR "trigger* neuropathology" OR "trigger* diabetes" OR "trigger* hypertension" OR "trigger* high cholesterol" OR "trigger* hypercholesterolemia" OR "trigger* obesity" OR "trigger* metabolic syndrome" OR "accelerat* Alzheimer*" OR "accelerat* dementia" OR "accelerat* cognitive decline" OR "accelerat* brain* decline" OR "accelerat* functional decline" OR "accelerat* memory decline" OR "accelerat* cognitive deficit*" OR "accelerat* language deficit*" OR "accelerat* memory deficit*" OR "accelerat* plasticity deficit*" OR "accelerat* behavioral deficit*" OR "accelerat* saccade deficit*" OR "accelerat* learning deficit*" OR "accelerat* neuropsychological deficit*" OR "accelerat* cognitive impair*" OR "accelerat* vascular impair*" OR "accelerat* memory impair*" OR "accelerat* neurogenesis impair*" OR "accelerat* neuropsychological impair*" OR "accelerat* mind impair*" OR "accelerat* functional impair*" OR "accelerat* learning impair*" OR "accelerat* executive function impair*" OR "accelerat* cognitive loss*" OR "accelerat*

neuronal loss*" OR "accelerat* synaptic loss*" OR "accelerat* memory loss*" OR "accelerat* loss of memory" OR "accelerat* hearing loss*" OR "accelerat* volume loss*" OR "accelerat* Impair* face recognition" OR "accelerat* Impair* reasoning" OR "accelerat* Impair* judgment" OR "accelerat* Impair* problem solving" OR "accelerat* inflamm*" OR "accelerat* oxidative stress" OR "accelerat* neuropathology" OR "accelerat* diabetes" OR "accelerat* hypertension" OR "accelerat* high cholesterol" OR "accelerat* hypercholesterolemia" OR "accelerat* obesity" OR "accelerat* metabolic syndrome" OR "Alzheimer* * caused by" OR "dementia caused by" OR "cognitive decline caused by" OR "brain* decline caused by" OR "functional decline caused by" OR "memory decline caused by" OR "cognitive deficit* caused by" OR "language deficit* caused by" OR "memory deficit* caused by" OR "plasticity deficit* caused by" OR "behavioral deficit* caused by" OR "saccade deficit* caused by" OR "learning deficit* caused by" OR "neuropsychological deficit* caused by" OR "cognitive impair* caused by" OR "vascular impair* caused by" OR "memory impair* caused by" OR "neurogenesis impair* caused by" OR "neuropsychological impair* caused by" OR "mind impair* caused by" OR "functional impair* caused by" OR "learning impair* caused by" OR " executive function impair* caused by" OR "cognitive loss* caused by" OR "neuronal loss* caused by" OR "synaptic loss* caused by" OR "memory loss* caused by" OR "loss of memory caused by" OR "hearing loss* caused by" OR "volume loss* caused by" OR "Impair* face recognition caused by" OR "Impair* reasoning caused by" OR "Impair* judgment caused by" OR "Impair* problem solving caused by" OR "inflamm* caused by" OR "oxidative stress caused by" OR "neuropathology caused by" OR "diabetes caused by" OR "hypertension caused by" OR "high cholesterol caused by" OR "hypercholesterolemia caused by" OR "obesity caused by" OR "metabolic syndrome caused by" OR "Alzheimer* * induced by" OR "dementia induced by" OR "cognitive decline induced by" OR "brain* decline induced by" OR "functional decline induced by" OR "memory decline induced by" OR "cognitive deficit* induced by" OR "language deficit* induced by" OR "memory deficit* induced by" OR "plasticity deficit* induced by" OR "behavioral deficit* induced by" OR "saccade deficit* induced by" OR "learning deficit* induced by" OR "neuropsychological deficit* induced by" OR "cognitive impair* induced by" OR "vascular impair* induced by" OR "memory impair* induced by" OR "neurogenesis impair* induced by" OR "neuropsychological impair* induced by" OR "mind impair* induced by" OR "functional impair* induced by" OR "learning impair* induced by" OR " executive function impair* induced by" OR "cognitive loss* induced by" OR "neuronal loss* induced by" OR "synaptic loss* induced by" OR "memory loss* induced by" OR "loss of memory induced by" OR "hearing loss* induced by" OR "volume loss* induced by" OR "Impair* face recognition induced by" OR "Impair* reasoning induced by" OR "Impair* judgment induced by" OR "Impair* problem solving induced by" OR "inflamm* induced by" OR "oxidative stress induced by" OR "neuropathology induced by" OR "diabetes induced by" OR "hypertension induced by" OR "high cholesterol induced by" OR "hypercholesterolemia induced by" OR "obesity induced by" OR "metabolic syndrome induced by")

AND

MESH HEADING NO EXPLODE

Antineoplastic Agents OR Anticoagulants OR Antineoplastic Combined Chemotherapy Protocols OR Anti-Inflammatory Agents, Non-Steroidal OR Hypoglycemic Agents OR Anti-Bacterial Agents OR Antipsychotic Agents OR Immunosuppressive Agents OR Anticonvulsants OR Platelet Aggregation Inhibitors OR Glucocorticoids OR Analgesics, Opioid OR Drug-Related Side Effects and Adverse Reactions OR Warfarin OR Analgesics OR Doxorubicin OR Cisplatin OR Protein Kinase Inhibitors OR Fibrinolytic Agents OR

Fluorouracil OR Antirheumatic Agents OR Antihypertensive Agents OR Pyridines OR Cyclophosphamide OR Bone Density Conservation Agents OR Antiviral Agents OR Bleomycin OR Antidepressive Agents OR Serotonin Uptake Inhibitors OR Thiophenes OR Antibiotics, Antineoplastic OR Angiogenesis Inhibitors OR Drug Hypersensitivity OR Proton Pump Inhibitors OR Deoxycytidine OR Ticlopidine OR Organoplatinum Compounds OR Anti-Arrhythmia Agents OR Angiotensin-Converting Enzyme Inhibitors OR Anti-HIV Agents OR Paclitaxel OR Chemotherapy, Adjuvant OR Acetaminophen OR Quinazolines OR Taxoids OR Vasodilator Agents OR Pilocarpine OR Triazoles OR Benzodiazepines OR Anti-Infective Agents OR Estrogens OR Thiazolidinediones OR Antineoplastic Agents, Hormonal OR Antineoplastic Agents, Phytogenic OR Cyclooxygenase 2 Inhibitors OR Anti-Ulcer Agents OR Cyclosporine OR Vasoconstrictor Agents OR Anthracyclines OR Anticarcinogenic Agents OR Convulsants OR Calcium Channel Blockers OR Cardiotonic Agents OR Dermatologic Agents OR Isoproterenol OR Antifungal Agents OR Ribavirin OR Antiparkinson Agents OR Clozapine OR Carboplatin OR Tamoxifen OR Antiretroviral Therapy, Highly Active OR Vincristine OR Cholinesterase Inhibitors OR Antidepressive Agents, Second-Generation OR Antitubercular Agents OR Hypolipidemic Agents OR Antineoplastic Agents, Alkylating OR Gastrointestinal Agents OR Aromatase Inhibitors OR Antithyroid Agents OR Organophosphonates OR Cyclooxygenase Inhibitors OR Antidepressive Agents, Tricyclic OR Antimanic Agents OR Phosphodiesterase 5 Inhibitors OR Dipeptidyl-Peptidase IV Inhibitors OR Anti-Retroviral Agents OR Methyl Ethers OR Chelating Agents OR Anticholesteremic Agents OR Contraceptive Agents, Female OR Anti-Asthmatic Agents OR Dopamine Uptake Inhibitors OR HIV Protease Inhibitors OR N-Methyl-3,4-methylenedioxyamphetamine OR Mycophenolic Acid OR Bronchodilator Agents OR Hydroxychloroquine OR Neurotransmitter Agents OR Anti-Obesity Agents OR Anabolic Agents OR Anesthetics OR Cardiovascular Agents OR Histone Deacetylase Inhibitors OR Alkylating Agents OR Chloroquine OR Antifibrinolytic Agents OR Benzoxazines OR Protease Inhibitors OR Fertility Agents, Female OR Dopamine Agents OR Anti-Infective Agents, Local OR Reverse Transcriptase Inhibitors OR Neuromuscular Agents OR Anti-Allergic Agents OR Monoamine Oxidase Inhibitors OR Neuromuscular Nondepolarizing Agents OR Nootropic Agents OR Photosensitizing Agents OR 5-alpha Reductase Inhibitors OR Sweetening Agents OR Sensory System Agents OR Adrenergic Agents OR Adrenergic Uptake Inhibitors OR Indicators and Reagents OR Antitussive Agents OR Surface-Active Agents OR Antimutagenic Agents

OR

MESH TERMS CHEMICALS

3B4a - TITLE

("poison*" OR "ecotoxologic* effect*" OR "occupation*" OR pollut* OR "*virus*" OR environmental OR "induc*" OR "damage-caus*" OR "drug*-caus*" OR "infect*-caus*" OR "chemotherapy-caus*" OR "treat*-caus*" OR "anesthesia-caus*" OR "chemical*-caus*" OR "cytokine*-caus*" OR "surg*-caus*" OR "radiation-caus*" OR "steroid-caus*" OR "mechanically-caus*" OR "promot* progression" OR "caus* accumulation" OR "caus* * accumulation" OR "progression of" OR expos* OR contamina* OR chemicals OR abuse* OR induc* OR "long-term effect*" OR "inhibit* *protection" OR dysfunction* OR aggregation OR accumulation OR "disease link* to" OR "chemical initiator*" OR "stimulat* microglia" OR "activat* microglia" OR "increas* risk*" OR "increas* the risk*" OR "adverse event*" OR "adverse reaction*" OR "adverse * event*" OR "adverse * reaction" OR "adverse effect*" OR "adverse * effect*" OR

hypersensitivity OR aggravat* OR exacerbat* OR detriment* OR *TOXI* OR "caus* * degrad*" OR "increas* * degrad*" OR "caus* * damag*" OR "increas* * damag*" OR "*toxi* caus* by" OR "*toxi* increas* by" OR "*toxi* produc* by" OR "*toxi* enhanc* by" OR "*toxi* stimulat* by" OR "*toxi* accelerat* by" OR "damag* caus* by" OR "*damag* increas* by" OR deleterious OR deteriorat* OR trigger* OR worsen* OR harm* OR hazard* OR "side-effect*" OR dangerous OR destructive OR injurious OR unsafe)

AND

MESH HEADING NO EXPLODE

Lipopolysaccharides OR Malondialdehyde OR Neurotoxicity Syndromes OR Carbon Tetrachloride OR Formaldehyde OR 9,10-Dimethyl-1,2-benzanthracene OR Trinitrobenzenesulfonic Acid OR Insecticides OR Endocrine Disruptors OR Diethylnitrosamine OR Hydrogen Peroxide OR Benzhydryl Compounds OR Chemical Warfare Agents OR Asbestos OR Herbicides OR Organometallic Compounds OR Scopolamine Hydrobromide OR Silicon Dioxide OR Polychlorinated Biphenyls OR 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine OR Benzo(a)pyrene OR Fluorocarbons OR Nitrogen Dioxide OR Polycyclic Hydrocarbons, Aromatic OR Tetrachlorodibenzodioxin OR Metals, Heavy OR Hydrocarbons, Chlorinated OR Chemical Industry OR 1,2-Dimethylhydrazine OR Ethylene Glycol OR Nitrosamines OR Benzene OR Fluorides OR Agricultural Workers' Diseases OR Bromodeoxyuridine OR Chromium OR Organophosphorus Compounds OR Organic Chemicals OR Carbon Monoxide OR Benzalkonium Compounds OR Chlorpyrifos OR Organophosphates OR Organophosphate Poisoning OR Volatile Organic Compounds OR Diethylhexyl Phthalate OR Sulfur Dioxide OR Petroleum OR Methylmercury Compounds OR Chlorine OR Dichlorodiphenyl Dichloroethylene OR Hydrocarbons OR Trichloroethylene OR Carbon Tetrachloride Poisoning OR 3,4-Dihydroxyphenylacetic Acid OR Alkanesulfonic Acids OR Plasticizers OR Halogenated Diphenyl Ethers OR Benzene Derivatives OR Dinitrofluorobenzene OR Toluene 2,4-Diisocyanate OR Benzopyrenes OR Cyclohexenes OR Nitrobenzenes OR Plastics OR Trihalomethanes OR Hydrocarbons, Brominated

OR

3B4b. TOPIC

("increas* amyloid-beta" OR "increas* beta-amyloid" OR "increas* abeta" OR "increas* senile plaque*" OR "increas* tau aggregat*" OR "increas* T-tau" OR "increas* P-tau" OR "increas*total tau" OR "increas* phospho-tau" OR "increas* tau protein*" OR "increas* hyperphosphorylated tau" OR "increas* neurofibrillary tangle*" OR "enhanc* amyloid-beta" OR "enhanc* beta-amyloid" OR "enhanc* abeta" OR "enhanc* senile plaque*" OR "enhanc* tau aggregat*" OR "enhanc* T-tau" OR "enhanc* P-tau" OR "enhanc*total tau" OR "enhanc* phospho-tau" OR "enhanc* tau protein*" OR "enhanc* hyperphosphorylated tau" OR "enhanc* neurofibrillary tangle*" OR "stimulat* amyloid-beta" OR "stimulat* beta-amyloid" OR "stimulat* abeta" OR "stimulat* senile plaque*" OR "stimulat* tau aggregat*" OR "stimulat* T-tau" OR "stimulat* P-tau" OR "stimulat*total tau" OR "stimulat* phospho-tau" OR "stimulat* tau protein*" OR "stimulat* hyperphosphorylated tau" OR "stimulat* neurofibrillary tangle*" OR "elevat* amyloid-beta" OR "elevat* beta-amyloid" OR "elevat* abeta" OR "elevat* senile plaque*" OR "elevat* tau aggregat*" OR "elevat* T-tau" OR "elevat* P-tau" OR "elevat*total tau" OR "elevat* phospho-tau" OR "elevat* tau protein*" OR "elevat* hyperphosphorylated tau" OR "elevat*

neurofibrillary tangle*" OR "induc* amyloid-beta" OR "induc* beta-amyloid" OR "induc* abeta" OR "induc* senile plaque*" OR "induc* tau aggregat*" OR "induc* T-tau" OR "induc* P-tau" OR "induc*total tau" OR "induc* phospho-tau" OR "induc* tau protein*" OR "induc* hyperphosphorylated tau" OR "induc* neurofibrillary tangle*" OR "produc* amyloid-beta" OR "produc* beta-amyloid" OR "produc* abeta" OR "produc* senile plaque*" OR "produc* tau aggregat*" OR "produc* T-tau" OR "produc* P-tau" OR "produc*total tau" OR "produc* phospho-tau" OR "produc* tau protein*" OR "produc* hyperphosphorylated tau" OR "produc* neurofibrillary tangle*" OR "accelerat* amyloid-beta" OR "accelerat* beta-amyloid" OR "accelerat* abeta" OR "accelerat* senile plaque*" OR "accelerat* tau aggregat*" OR "accelerat* T-tau" OR "accelerat* P-tau" OR "accelerat*total tau" OR "accelerat* phospho-tau" OR "accelerat* tau protein*" OR "accelerat* hyperphosphorylated tau" OR "accelerat* neurofibrillary tangle*" OR "amyloid-beta induc* by" OR "beta-amyloid induc* by" OR "abeta induc* by" OR "senile plaque* induc* by" OR "tau aggregat* induc* by" OR "T-tau induc* by" OR "P-tau induc* by" OR "total tau induc* by" OR "phospho-tau induc* by" OR "tau protein* induc* by" OR "hyperphosphorylated tau induc* by" OR "neurofibrillary tangle* induc* by" OR "amyloid-beta produc* by" OR "beta-amyloid produc* by" OR "abeta produc* by" OR "senile plaque* produc* by" OR "tau aggregat* produc* by" OR "T-tau produc* by" OR "P-tau produc* by" OR "total tau produc* by" OR "phospho-tau produc* by" OR "tau protein* produc* by" OR "hyperphosphorylated tau produc* by" OR "neurofibrillary tangle* produc* by" OR "caus* Alzheimer*" OR "caus* dementia" OR "caus* cognitive decline" OR "caus* brain* decline" OR "caus* functional decline" OR "caus* memory decline" OR "caus* cognitive deficit*" OR "caus* language deficit*" OR "caus* memory deficit*" OR "caus* plasticity deficit*" OR "caus* behavioral deficit*" OR "caus* saccade deficit*" OR "caus* learning deficit*" OR "caus* neuropsychological deficit*" OR "caus* cognitive impair*" OR "caus* vascular impair*" OR "caus* memory impair*" OR "caus* neurogenesis impair*" OR "caus* neuropsychological impair*" OR "caus* mind impair*" OR "caus* functional impair*" OR "caus* learning impair*" OR "caus* executive function impair*" OR "caus* cognitive loss*" OR "caus* neuronal loss*" OR "caus* synaptic loss*" OR "caus* memory loss*" OR "caus* loss of memory" OR "caus* hearing loss*" OR "caus* volume loss*" OR "caus* Impair* face recognition" OR "caus* Impair* reasoning" OR "caus* Impair* judgment" OR "caus* Impair* problem solving" OR "caus* inflamm*" OR "caus* oxidative stress" OR "caus* neuropathology" OR "caus* diabetes" OR "caus* hypertension" OR "caus* high cholesterol" OR "caus* hypercholesterolemia" OR "caus* obesity" OR "caus* metabolic syndrome" OR "induc* Alzheimer*" OR "induc* dementia" OR "induc* cognitive decline" OR "induc* brain* decline" OR "induc* functional decline" OR "induc* memory decline" OR "induc* cognitive deficit*" OR "induc* language deficit*" OR "induc* memory deficit*" OR "induc* plasticity deficit*" OR "induc* behavioral deficit*" OR "induc* saccade deficit*" OR "induc* learning deficit*" OR "induc* neuropsychological deficit*" OR "induc* cognitive impair*" OR "induc* vascular impair*" OR "induc* memory impair*" OR "induc* neurogenesis impair*" OR "induc* neuropsychological impair*" OR "induc* mind impair*" OR "induc* functional impair*" OR "induc* learning impair*" OR "induc* executive function impair*" OR "induc* cognitive loss*" OR "induc* neuronal loss*" OR "induc* synaptic loss*" OR "induc* memory loss*" OR "induc* loss of memory" OR "induc* hearing loss*" OR "induc* volume loss*" OR "induc* Impair* face recognition" OR "induc* Impair* reasoning" OR "induc* Impair* judgment" OR "induc* Impair* problem solving" OR "induc* inflamm*" OR "induc* oxidative stress" OR "induc* neuropathology" OR "induc* diabetes" OR "induc* hypertension" OR "induc* high cholesterol" OR "induc* hypercholesterolemia" OR "induc* obesity" OR "induc* metabolic syndrome" OR "produc* Alzheimer*" OR "produc* dementia" OR

"produc* cognitive decline" OR "produc* brain* decline" OR "produc* functional decline" OR "produc* memory decline" OR "produc* cognitive deficit*" OR "produc* language deficit*" OR "produc* memory deficit*" OR "produc* plasticity deficit*" OR "produc* behavioral deficit*" OR "produc* saccade deficit*" OR "produc* learning deficit*" OR "produc* neuropsychological deficit*" OR "produc* cognitive impair*" OR "produc* vascular impair*" OR "produc* memory impair*" OR "produc* neurogenesis impair*" OR "produc* neuropsychological impair*" OR "produc* mind impair*" OR "produc* functional impair*" OR "produc* learning impair*" OR "produc* executive function impair*" OR "produc* cognitive loss*" OR "produc* neuronal loss*" OR "produc* synaptic loss*" OR "produc* memory loss*" OR "produc* loss of memory" OR "produc* hearing loss*" OR "produc* volume loss*" OR "produc* Impair* face recognition" OR "produc* Impair* reasoning" OR "produc* Impair* judgment" OR "produc* Impair* problem solving" OR "produc* inflamm*" OR "produc* oxidative stress" OR "produc* neuropathology" OR "produc* diabetes" OR "produc* hypertension" OR "produc* high cholesterol" OR "produc* hypercholesterolemia" OR "produc* obesity" OR "produc* metabolic syndrome" OR "increas* Alzheimer*" OR "increas* dementia" OR "increas* cognitive decline" OR "increas* brain* decline" OR "increas* functional decline" OR "increas* memory decline" OR "increas* cognitive deficit*" OR "increas* language deficit*" OR "increas* memory deficit*" OR "increas* plasticity deficit*" OR "increas* behavioral deficit*" OR "increas* saccade deficit*" OR "increas* learning deficit*" OR "increas* neuropsychological deficit*" OR "increas* cognitive impair*" OR "increas* vascular impair*" OR "increas* memory impair*" OR "increas* neurogenesis impair*" OR "increas* neuropsychological impair*" OR "increas* mind impair*" OR "increas* functional impair*" OR "increas* learning impair*" OR "increas* executive function impair*" OR "increas* cognitive loss*" OR "increas* neuronal loss*" OR "increas* synaptic loss*" OR "increas* memory loss*" OR "increas* loss of memory" OR "increas* hearing loss*" OR "increas* volume loss*" OR "increas* Impair* face recognition" OR "increas* Impair* reasoning" OR "increas* Impair* judgment" OR "increas* Impair* problem solving" OR "increas* inflamm*" OR "increas* oxidative stress" OR "increas* neuropathology" OR "increas* diabetes" OR "increas* hypertension" OR "increas* high cholesterol" OR "increas* hypercholesterolemia" OR "increas* obesity" OR "increas* metabolic syndrome" OR "exacerbat* Alzheimer*" OR "exacerbat* dementia" OR "exacerbat* cognitive decline" OR "exacerbat* brain* decline" OR "exacerbat* functional decline" OR "exacerbat* memory decline" OR "exacerbat* cognitive deficit*" OR "exacerbat* language deficit*" OR "exacerbat* memory deficit*" OR "exacerbat* plasticity deficit*" OR "exacerbat* behavioral deficit*" OR "exacerbat* saccade deficit*" OR "exacerbat* learning deficit*" OR "exacerbat* neuropsychological deficit*" OR "exacerbat* cognitive impair*" OR "exacerbat* vascular impair*" OR "exacerbat* memory impair*" OR "exacerbat* neurogenesis impair*" OR "exacerbat* neuropsychological impair*" OR "exacerbat* mind impair*" OR "exacerbat* functional impair*" OR "exacerbat* learning impair*" OR "exacerbat* executive function impair*" OR "exacerbat* cognitive loss*" OR "exacerbat* neuronal loss*" OR "exacerbat* synaptic loss*" OR "exacerbat* memory loss*" OR "exacerbat* loss of memory" OR "exacerbat* hearing loss*" OR "exacerbat* volume loss*" OR "exacerbat* Impair* face recognition" OR "exacerbat* Impair* reasoning" OR "exacerbat* Impair* judgment" OR "exacerbat* Impair* problem solving" OR "exacerbat* inflamm*" OR "exacerbat* oxidative stress" OR "exacerbat* neuropathology" OR "exacerbat* diabetes" OR "exacerbat* hypertension" OR "exacerbat* high cholesterol" OR "exacerbat* hypercholesterolemia" OR "exacerbat* obesity" OR "exacerbat* metabolic syndrome" OR "trigger* Alzheimer*" OR "trigger* dementia" OR "trigger* cognitive decline" OR "trigger* brain* decline" OR "trigger* functional decline" OR "trigger*

memory decline" OR "trigger* cognitive deficit*" OR "trigger* language deficit*" OR "trigger* memory deficit*" OR "trigger* plasticity deficit*" OR "trigger* behavioral deficit*" OR "trigger* saccade deficit*" OR "trigger* learning deficit*" OR "trigger* neuropsychological deficit*" OR "trigger* cognitive impair*" OR "trigger* vascular impair*" OR "trigger* memory impair*" OR "trigger* neurogenesis impair*" OR "trigger* neuropsychological impair*" OR "trigger* mind impair*" OR "trigger* functional impair*" OR "trigger* learning impair*" OR "trigger* executive function impair*" OR "trigger* cognitive loss*" OR "trigger* neuronal loss*" OR "trigger* synaptic loss*" OR "trigger* memory loss*" OR "trigger* loss of memory" OR "trigger* hearing loss*" OR "trigger* volume loss*" OR "trigger* Impair* face recognition" OR "trigger* Impair* reasoning" OR "trigger* Impair* judgment" OR "trigger* Impair* problem solving" OR "trigger* inflamm*" OR "trigger* oxidative stress" OR "trigger* neuropathology" OR "trigger* diabetes" OR "trigger* hypertension" OR "trigger* high cholesterol" OR "trigger* hypercholesterolemia" OR "trigger* obesity" OR "trigger* metabolic syndrome" OR "accelerat* Alzheimer*" OR "accelerat* dementia" OR "accelerat* cognitive decline" OR "accelerat* brain* decline" OR "accelerat* functional decline" OR "accelerat* memory decline" OR "accelerat* cognitive deficit*" OR "accelerat* language deficit*" OR "accelerat* memory deficit*" OR "accelerat* plasticity deficit*" OR "accelerat* behavioral deficit*" OR "accelerat* saccade deficit*" OR "accelerat* learning deficit*" OR "accelerat* neuropsychological deficit*" OR "accelerat* cognitive impair*" OR "accelerat* vascular impair*" OR "accelerat* memory impair*" OR "accelerat* neurogenesis impair*" OR "accelerat* neuropsychological impair*" OR "accelerat* mind impair*" OR "accelerat* functional impair*" OR "accelerat* learning impair*" OR "accelerat* executive function impair*" OR "accelerat* cognitive loss*" OR "accelerat* neuronal loss*" OR "accelerat* synaptic loss*" OR "accelerat* memory loss*" OR "accelerat* loss of memory" OR "accelerat* hearing loss*" OR "accelerat* volume loss*" OR "accelerat* Impair* face recognition" OR "accelerat* Impair* reasoning" OR "accelerat* Impair* judgment" OR "accelerat* Impair* problem solving" OR "accelerat* inflamm*" OR "accelerat* oxidative stress" OR "accelerat* neuropathology" OR "accelerat* diabetes" OR "accelerat* hypertension" OR "accelerat* high cholesterol" OR "accelerat* hypercholesterolemia" OR "accelerat* obesity" OR "accelerat* metabolic syndrome" OR "Alzheimer* * caused by" OR "dementia caused by" OR "cognitive decline caused by" OR "brain* decline caused by" OR "functional decline caused by" OR "memory decline caused by" OR "cognitive deficit* caused by" OR "language deficit* caused by" OR "memory deficit* caused by" OR "plasticity deficit* caused by" OR "behavioral deficit* caused by" OR "saccade deficit* caused by" OR "learning deficit* caused by" OR "neuropsychological deficit* caused by" OR "cognitive impair* caused by" OR "vascular impair* caused by" OR "memory impair* caused by" OR "neurogenesis impair* caused by" OR "neuropsychological impair* caused by" OR "mind impair* caused by" OR "functional impair* caused by" OR "learning impair* caused by" OR " executive function impair* caused by" OR "cognitive loss* caused by" OR "neuronal loss* caused by" OR "synaptic loss* caused by" OR "memory loss* caused by" OR "loss of memory caused by" OR "hearing loss* caused by" OR "volume loss* caused by" OR "Impair* face recognition caused by" OR "Impair* reasoning caused by" OR "Impair* judgment caused by" OR "Impair* problem solving caused by" OR "inflamm* caused by" OR "oxidative stress caused by" OR "neuropathology caused by" OR "diabetes caused by" OR "hypertension caused by" OR "high cholesterol caused by" OR "hypercholesterolemia caused by" OR "obesity caused by" OR "metabolic syndrome caused by" OR "Alzheimer* * induced by" OR "dementia induced by" OR "cognitive decline induced by" OR "brain* decline induced by" OR "functional decline induced by" OR "memory decline induced by" OR "cognitive deficit* induced by" OR "language deficit* induced by" OR "memory deficit*

induced by" OR "plasticity deficit* induced by" OR "behavioral deficit* induced by" OR "saccade deficit* induced by" OR "learning deficit* induced by" OR "neuropsychological deficit* induced by" OR "cognitive impair* induced by" OR "vascular impair* induced by" OR "memory impair* induced by" OR "neurogenesis impair* induced by" OR "neuropsychological impair* induced by" OR "mind impair* induced by" OR "functional impair* induced by" OR "learning impair* induced by" OR " executive function impair* induced by" OR "cognitive loss* induced by" OR "neuronal loss* induced by" OR "synaptic loss* induced by" OR "memory loss* induced by" OR "loss of memory induced by" OR "hearing loss* induced by" OR "volume loss* induced by" OR "Impair* face recognition induced by" OR "Impair* reasoning induced by" OR "Impair* judgment induced by" OR "Impair* problem solving induced by" OR "inflamm* induced by" OR "oxidative stress induced by" OR "neuropathology induced by" OR "diabetes induced by" OR "hypertension induced by" OR "high cholesterol induced by" OR "hypercholesterolemia induced by" OR "obesity induced by" OR "metabolic syndrome induced by")

AND

MESH HEADING NO EXPLODE

Lipopolysaccharides OR Malondialdehyde OR Neurotoxicity Syndromes OR Carbon Tetrachloride OR Formaldehyde OR 9,10-Dimethyl-1,2-benzanthracene OR Trinitrobenzenesulfonic Acid OR Insecticides OR Endocrine Disruptors OR Diethylnitrosamine OR Hydrogen Peroxide OR Benzhydryl Compounds OR Chemical Warfare Agents OR Asbestos OR Herbicides OR Organometallic Compounds OR Scopolamine Hydrobromide OR Silicon Dioxide OR Polychlorinated Biphenyls OR 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine OR Benzo(a)pyrene OR Fluorocarbons OR Nitrogen Dioxide OR Polycyclic Hydrocarbons, Aromatic OR Tetrachlorodibenzodioxin OR Metals, Heavy OR Hydrocarbons, Chlorinated OR Chemical Industry OR 1,2-Dimethylhydrazine OR Ethylene Glycol OR Nitrosamines OR Benzene OR Fluorides OR Agricultural Workers' Diseases OR Bromodeoxyuridine OR Chromium OR Organophosphorus Compounds OR Organic Chemicals OR Carbon Monoxide OR Benzalkonium Compounds OR Chlorpyrifos OR Organophosphates OR Organophosphate Poisoning OR Volatile Organic Compounds OR Diethylhexyl Phthalate OR Sulfur Dioxide OR Petroleum OR Methylmercury Compounds OR Chlorine OR Dichlorodiphenyl Dichloroethylene OR Hydrocarbons OR Trichloroethylene OR Carbon Tetrachloride Poisoning OR 3,4-Dihydroxyphenylacetic Acid OR Alkanesulfonic Acids OR Plasticizers OR Halogenated Diphenyl Ethers OR Benzene Derivatives OR Dinitrofluorobenzene OR Toluene 2,4-Diisocyanate OR Benzopyrenes OR Cyclohexenes OR Nitrobenzenes OR Plastics OR Trihalomethanes OR Hydrocarbons, Brominated

SDM-2A - Appendix 2 - Streamlined Approach - Unambiguous MeSH Terms

("Drug-Related Side Effects AND Adverse Reactions" OR Abnormalities, Drug Induced OR Abnormalities, Radiation-Induced OR Agricultural Workers Diseases OR Aids Related Opportunistic Infections OR Air Pollutants OR Air Pollutants, Occupational OR Air Pollutants, Radioactive OR Air Pollution OR Air Pollution, Indoor OR Air Pollution, Radioactive OR Alcohol Drinking OR Alcohol Related Disorders OR Alcoholic Beverages OR Alcoholic Intoxication OR Alcoholism OR Amphetamine Related Disorders OR Amphetamines OR Arsenic Poisoning OR Asthma, Aspirin-Induced OR Asthma, Exercise-Induced OR Asthma, Occupational OR Behavior, Addictive OR Bullying OR Cadmium Poisoning OR Carbon Monoxide

Poisoning OR Carbon Tetrachloride Poisoning OR Carcinogenicity Tests OR Carcinogens OR Carcinogens, Environmental OR Causality OR Cardiomegaly, Exercise-Induced OR Chemical Warfare Agents OR Chemically-Induced Disorders OR Child Abuse OR Child Abuse, Sexual OR Cholesterol, Dietary OR Ciguatera Poisoning OR Cocaine Related Disorders OR Cytomegalovirus Infections OR Dermatitis, Occupational OR Diet, Atherogenic OR Diet, High Fat OR Dietary Carbohydrates OR Dietary Fats OR Dietary Fats, Unsaturated OR Dietary Fiber OR Dietary Sucrose OR Domestic Violence OR Drug Contamination OR Drug Eruptions OR Drug Hypersensitivity OR Drug Overdose OR Drug-Induced Liver Injury OR Dyskinesia, Drug Induced OR Eating Disorders OR Environmental Exposure OR Environmental Illness OR Environmental Pollutants OR Environmental Pollution OR Environmental Pollution OR Escherichia Coli Infections OR Fast Foods OR Fluoride Poisoning OR Food Additives OR Food Contamination OR Food Hypersensitivity OR Foodborne Diseases OR Gas Poisoning OR Hazardous Substances OR Hazardous Waste OR Hearing Loss, Noise Induced OR Heavy Metal Poisoning, Nervous System OR Hepatitis A, Chronic OR Hepatitis B, Chronic OR Hepatitis C, Chronic OR Heroin Dependence OR Herpesviridae Infections OR Htlv I Infections OR Hypersensitivity OR Hypersensitivity, Delayed OR Hypersensitivity, Immediate OR Iatrogenic Disease OR Inhalation Exposure OR Iron Overload OR Lead Poisoning OR Lead Poisoning, Nervous System OR Lead Poisoning, Nervous System, Adult OR Lead Poisoning, Nervous System, Childhood OR Leukemia, Radiation Induced OR Manganese Poisoning OR Marijuana Abuse OR Maternal Exposure OR Mercury Poisoning OR Mercury Poisoning, Nervous System OR Morphine Dependence OR Mptp Poisoning OR Mushroom Poisoning OR Mutagenicity Tests OR Mutagens OR Neoplasms, Radiation Induced OR Neurotoxicity Syndromes OR Occupational Diseases OR Occupational Exposure OR Opioid Related Disorders OR Opportunistic Infections OR Organophosphate Poisoning OR Paternal Exposure OR Plant Poisoning OR Pneumonia, Ventilator-Associated OR Poisoning OR Poisons OR Prenatal Exposure Delayed Effects OR Psychoses, Substance Induced OR Radiation Effects OR Radiation Injuries OR Radioactive Hazard Release OR Radioactive Pollutants OR Respiratory Hypersensitivity OR Salmonella Food Poisoning OR Sedentary Lifestyle OR Shellfish Poisoning OR Sleep Deprivation OR Sleep Disorders OR Sodium Chloride, Dietary OR Sodium, Dietary OR Soil Pollutants OR Soil Pollutants, Radioactive OR Spouse Abuse OR Staphylococcal Food Poisoning OR Staphylococcal Infections OR Streptococcal Infections OR Substance Abuse, Intravenous OR Substance Withdrawal Syndrome OR Substance-Related Disorders OR Teratogens OR Tobacco Smoke Pollution OR Tobacco Use Disorder OR Toxicity Tests, Chronic OR Virus Diseases OR Vitamin D Deficiency OR Water Pollutants OR Water Pollutants, Chemical OR Water Pollutants, Radioactive OR Water Pollution OR Water Pollution, Chemical)

6A2. Strategy

The overall strategy for identifying AD causes, treatments, and characteristics was essentially the same, although the implementation of the strategy differed slightly as we gained knowledge during the evolution of the study. The strategy components are:

- Select source database (Medline/Pubmed was selected as the primary source database, although the Thomson-Reuters version was used when proximity searching was performed).
- Generate a core AD database (a Pubmed query was used to generate a core AD database).

- Retrieve records relevant to AD treatments (or AD causes or AD characteristics) from the core AD database (a combination of MeSH-based, text-based, and visual examination approaches was used to retrieve records relevant to AD treatments, AD causes, and AD characteristics, and to extract the desired AD treatments, AD causes, and AD characteristics from these retrieved records).

6B. Methodology for Identifying Existing AD Treatments

6B1. Overview

To identify existing AD treatments, a query consisting of MeSH terms and text terms was developed to retrieve Medline records that had high probability of describing AD treatments. These retrieved Medline records were imported into our VP text mining software [2] and parsed into phrases. Many of these parsed record abstract phrases were visually inspected to identify existing AD treatments and identify consequences of those treatments (e.g., increased cerebral blood flow, reduced Abeta, reduced tau hyperphosphorylation, etc).

6B2. Identifying Existing AD Treatments

6B2a. MeSH-based Approach

The MeSH-based approach consisted of two components: MeSH Qualifiers related to treatments/therapies relatively strongly (e.g., diet therapy, drug therapy, prevention & control, therapeutic use, therapy, etc), and MeSH Headings related to treatments/therapies relatively unambiguously (e.g., Treatment Outcome, Neuroprotective Agents, Nootropic Agents, Plant Extracts, Phytotherapy, Dietary Supplements, Drugs, Chinese Herbal, etc). Each of the two components was intersected with a core AD Medline query (e.g., Alzheimer* OR dementia OR "mild cognitive impairment") to retrieve records describing AD treatments. The retrieved records were inspected visually, and the relevant articles extracted.

As a very simple example of the above, a query term might be "diet therapy" in the MeSH Qualifier field, AND "Alzheimer's" in the title field.

6B2b. Text-based Approach

The text-based approach was developed and used because of the following MeSH-based approach limitations:

1) not all Medline records have MeSH terms assigned;

2) for those records with MeSH terms, the terms do not always form a comprehensive set;

3) for records with MeSH terms, the Qualifiers appended to the Heading are not always complete.

Thus, the text-based approach complements (and overlaps) the MeSH-based approach.

Fundamentally, the text-based approach 1) identified linking terms that were strongly associated with AD treatments and their consequences, and then 2) used these linking terms to search for the AD treatments and consequences of interest. These linking terms were obtained from reading the records retrieved with the MeSH-based approach, and selecting those terms strongly associated with AD treatments and their consequences. Some of the more useful linking terms identified included the following: treat*, therap*, prevent*, protect*, improv*, reduc*, attenuat*, ameliorat*, enhanc*, revers*, promot*, alleviat*, inhibit*, remov*, suppress*, mitigat*, restor*, lower*, preserv*, regenerat*, rescu*, slow*.

The text-based approach was used at three distinct points in the study:

1) It was used as part of the total AD Medline database query to retrieve records strongly associated with AD treatments.

2) It was applied to the parsed abstract phrases of the retrieved records imported into the VP software to surgically extract the existing AD treatments and their consequences.

3) It was used to develop patterns of terms for searching the non-AD Medline literature to generate literature-based discovery of potential AD treatments.

The main text mining advance in this study was development and demonstration of this AD treatment pattern filter for

1) querying the Medline database,

2) extracting AD treatments and their consequences from the parsed abstract phrases, and

3) discovering potential AD treatments from the non-AD biomedical literature.

The first chronological application of the linking terms was to help generate the initial query used for retrieving the AD treatment records from the Medline database. In the query, the linking terms were added to the MeSH terms described in 6B2a. The linking terms were only applied to the title field to minimize retrieval of excessive non-relevant records.

The second chronological application of the linking terms was to help extract existing AD treatments and their consequences from the parsed abstract phrases of the retrieved AD treatment records in the VP software. Approximately 52,000 records constituted the retrieved Medline AD treatments database, and approximately 3.5 million abstract phrases were parsed from the abstracts by the VP software. There was a dramatic increase in the number of phrases as the frequency of their appearance decreased. For example, there were 20,000 phrases that appeared in 22 records or more (roughly the number of phrases that were examined visually). There were 3,437,961 phrases that appeared in 21 records or less. In particular, there were 3,322,873 phrases that appeared in three records or less! It is these lower frequency phrases that may represent promising emerging AD treatments, or AD treatments that for one reason or another may have been suppressed in the literature.

The higher frequency phrases could be inspected visually, but a text mining filtering approach was necessary to extract the desired treatment and treatment consequence information from the millions of lower frequency phrases. Linking terms were used to search these lower frequency phrases and efficiently extract the requisite treatment and consequences information.

As a very simple example, we might search the ~3.5 million abstract phrases in the database of AD treatment records using the linking term "improv*". Typically, this term might appear in the larger text string of e.g. "substance X improved Abeta clearance". Thus, "substance X" would be the AD treatment identified, "Abeta" would be the AD characteristic of interest, and "Abeta clearance" would show the AD characteristic having moved in the desired direction. As the next paragraph will show, if the above text sub-string "improved Abeta clearance" were used to query the non-AD literature, then treatments/mechanisms from non-AD literatures could be identified and extrapolated (***'re-purposed'***) for possible use in treating/understanding AD pathology.

6C. Identify Potential AD Treatments (Discovery)

The third chronological application of the linking terms was for use as a query in literature-based discovery of potential AD treatments. Linking phrases that formed patterns characteristic of successful AD treatments were generated, and applied to the Medline non-AD literature. These linking phrases consisted of linking terms combined with the AD characteristics to which they were linked (e.g., *increase* glutathione, *inhibit* GSK-3, *increase* CREB phosphorylation, etc.) In practice, the linking phrases were constructed more broadly, such as *increas** NEAR/3 glutathione, *inhibit** NEAR/3 GSK-3, etc. For the literature-based discovery application, combinations of the more fundamental and less AD-specific linking phrases were used

(e.g., (((increas* OR enhanc* OR restor*) NEAR/3 "norepinephrine") AND ((increas* OR enhanc* OR restor*) NEAR/3 "Nrf2")) NOT ((alzheimer* OR dementia OR "mild cognitive impairment") OR {existing AD treatments}).

While terms such as 'reduce Abeta' or 'reduce tau phosphorylation' may be efficient for extracting existing AD treatments from the AD literature, they are very inefficient, either in isolation or especially in combination, for AD treatment discovery from the non-AD literature. It is difficult to imagine people doing research in reducing Abeta or reducing tau hyperphosphorylation not emphasizing the AD/dementia applications in their publications.

6D. Identify Existing AD Characteristics

Existing AD characteristics were identified mainly using the text-based approach. The first step in this approach was reading thousands of higher frequency abstract phrases parsed from treatment records retrieved with the MeSH-based query, as described in section 6B2b. This step had two benefits: identifying the higher frequency AD characteristics, and identifying terms closely linked to those characteristics.

Some of the more useful linking terms identified included the following: treat*, therap*, prevent*, protect*, improv*, reduc*, attenuat*, ameliorat*, enhanc*, revers*, promot*, alleviat*, inhibit*, remov*, suppress*, mitigat*, restor*, lower*, preserv*, regenerat*, rescu*, slow*, neuroprotect*, neurorestorati*, decreas*, increas*, eliminat*. Some of these terms had higher

efficiencies of identifying the treatment consequences of interest than others. Terms like prevent*, protect*, improv*, restor*, alleviat*, ameliorat*, mitigat*, etc, almost always gave the desired AD characteristics and the direction in which they changed as a result of treatment. Terms like decreas*, increas*, reduc*, etc, could go either way. The former group of terms had the 'sense' of ***improvement***, while the latter group of terms reflected ***change*** (positive or negative). In all cases, each retrieved phrase was validated before it could be included as an AD characteristic.

The second step was identifying the lower frequency AD characteristics. Many of the linking terms obtained in the first step were applied to all the abstract phrases in the full AD core Medline database, and ~250 major and semi-major existing AD characteristics were identified.

However,

- additional linking terms could have been identified;
- linking term patterns (combinations of linking terms) could have been identified for greater precision;
- not all linking terms identified were used;
- not all existing AD characteristics appeared in text in proximity to the identified linking terms;
- software limitations on extracted phrase length excluded those existing AD characteristics not in very close proximity to the identified linking terms.

An expanded study could easily overcome these limitations, and possibly double the number of existing AD characteristics identified.

6E. Identify Potential AD Characteristics (Discovery)

The concept is to identify patterns of AD characteristics that tend to co-occur frequently in the AD literature, then use these patterns as a search query in the non-AD literature. New patterns may be identified in the non-AD literature consisting of the search query pattern plus additional characteristics not in the AD literature. These additional characteristics would then be candidates for discovery as new AD characteristics that not have been identified previously.

For example, IL-1 and IL-6 and TNF-alpha and NF-KappaB tend to co-occur in many AD articles relating to inflammation. These four terms would be combined as a query for the non-AD literature: "IL-1 and IL-6 and TNF-alpha and NF-KappaB". Any records retrieved would be examined for additional characteristics, and these additional characteristics would be validated if they did not occur in the AD literature.

Myriad other patterns are possible. For example, existing AD treatments and existing AD causes move AD characteristics in known directions. Non-AD literatures could be searched for characteristics impacted by these known AD treatments and AD causes, and not contained in the core AD literature. Combinations of these AD treatments and AD causes could be used to increase the likelihood that any new characteristics identified would have higher relevance to AD.

As a specific example, consider the following query: (high-fat-diet* NEAR/5 (increas* OR decreas*) AND chitosan NEAR/5 (increas* OR decreas*)) NOT alzheimer*. This will retrieve all records reflecting an increase or decrease of characteristic values (in the non-AD literature) due to the presence of the existing AD cause "high-fat-diet" and the existing AD treatment "chitosan". Applying this query to the Medline database leads to the identification of a potential AD characteristic "mup17" (major urinary protein 17) [3]. This potential AD characteristic is not found in the AD literature, but it is altered in one direction by an existing AD cause, and is altered in the opposing direction by an existing AD treatment. So, it might be a valuable characteristic for AD researchers to track.

The number of existing AD characteristics identified appeared to be far more than could be used in practice. Therefore, identification of additional potential AD characteristics was not deemed a first-order priority in the present study. No attempt was made to identify specific potential AD characteristics, beyond the illustrative example above.

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APPENDIX 4 – PN/PAD CONTRIBUTING FACTOR AND TREATMENT IDENTIFICATION METHODOLOGY

6A2. Strategy

Table 6-1 - Approaches Used to Identify Causes/Treatments/Characteristics (Biomarkers/Symptoms)

APPROACH			
VISUAL INSPECTION ABSTRACT	X	X	X
LINKING TERMS TITLE	X	X	X
LINKING TERMS ABSTRACT	X	X	X
MESH TERMS UNAMBIGUOUS	X	X	X
MESH TERMS QUALIFIERS	X	X	X
DOT PRODUCT ABSTRACT	X		
CATEGORIES----->	**CAUSES**	**TREATMENTS**	**CHARACTERISTICS**

The overall conceptual strategy for identifying existing PN/PAD causes, treatments, and characteristics was based upon the conceptual strategy used in [Kostoff, Porter, Buchtel, 2018], although the implementation of the conceptual strategy differed slightly as knowledge was gained during the evolution of the study.

The strategy components used in the present study are:

- Select source database (Medline/Pubmed was selected as the primary source database, although the Thomson-Reuters version was used when proximity searching was performed).
- Generate a core PN/PAD database (a Pubmed query was used to generate a core PN/PAD database).
- Retrieve records relevant to PN/PAD treatments, contributing factors, or characteristics from the core PN/PAD database (methods will be shown in following sections)
- Extract existing contributing factors, treatments, and characteristics from retrieved records (methods will be shown in following sections)

A combination of MeSH-based and text-based examination approaches was used to retrieve records relevant to PN/PAD treatments, contributing factors, and characteristics, and to extract the desired PN/PAD treatments, contributing factors, and characteristics from these retrieved records. Table 6-1 summarizes the specific approaches used to identify contributing factors, treatments, and characteristics. Because of resource limitations, not all approaches were applied to all targets.

6B. Methodology for Identifying Existing and Potential PN/PAD Contributing Factors, Treatments, and Characteristics

6B1. Overview

As stated above, a MeSH-based approach and a text-based approach were used in tandem to identify existing PN/PAD contributing factors, treatments, and characteristics. The text-based approach was developed and used because of the following MeSH-based approach limitations:

1) not all Medline records have MeSH terms assigned;

2) for those records with MeSH terms, the terms do not always form a comprehensive set;

3) for records with MeSH terms, the Qualifiers appended to the Heading are not always complete.

Thus, the text-based approach complements (and overlaps) the MeSH-based approach.

6B2. Identifying Existing PN/PAD Contributing Factors

6B2a. Text-based Approach

6B2a1. Visual Inspection

The text-based approach had three components: a visual inspection component, a linking term component, and a dot-product component. The parsed Abstract field, containing about 4,000,000 phrases reflecting the 43056 records that constituted the core PN/PAD database, was used for all three components. The visual inspection component involved reading the 30,000 highest frequency Abstract phrases, and selecting those phrases deemed to be candidate contributing factors. The Vantage Point (VP) software [VP, 2019] containing these phrases displays both the phrases and the Titles and Abstracts of the records in which they appear. This allows validation of each candidate contributing factor selected.

6B2a2. Linking Term

To identify candidate contributing factors in the lower frequency portion of the parsed Abstract field, a text-mining approach was necessary. Linking terms strongly associated with contributing factors were generated through visually inspecting many records containing foundational contributing factors in the Titles, and identifying those terms that appeared frequently with the foundational contributing factors. The remainder of the parsed Abstract field was searched with use of these linking terms. The additional candidate contributing factors were extracted from the retrieved phrases, and validated as contributing factors.

These linking terms included: -induced; caused by; induced by; -contaminated; exposure to; exposure(s) [at end of phrase]; exposed to; poisoning [at end]; -exposed [at end]; -related; -associated; -infected; abuse*; toxicity; risk factors; deficiency; neurotoxicity; risk factor; causes; workers; toxic; occupational; intoxication; toxicities; neurotoxic; excessive; deficiencies; contributing factors; worker; contributing factor; occupation; overload.

6B2a3. Dot Product

While the visual inspection approach identifies comprehensively the higher-frequency foundational causes, the linking term approach is less efficient. Not all foundational causes are

associated with the finite list of linking terms used. Even if a foundational cause is associated (in the same Abstract) with a linking term, the software effectively limits the proximity of the linking term/foundational cause to four words. Some foundational causes can be located much further away from a linking term than four words in an Abstract.

To identify additional foundational causes that may have slipped through the cracks from the visual inspection and linking term approaches, the dot product approach was developed. Approximately 12,350 potentially toxic substances from myriad other sources (including past foundational causes studies, government-approved lists of toxic substances, MeSH-derived causes, etc) were generated, and intersected with the ~4,000,000 Abstract phrases in the core PN/PAD literature. While the dot product approach was developed specifically for identifying causes, a similar approach could be used for identifying treatments, biomarkers, mechanisms, etc. Moreover, given that many authors don't place detailed substances in the Title or Abstract, there could be substantial benefits gained by using full-text rather than Abstracts.

6B2b. MeSH-based Approach

6B2b1. MeSH Qualifiers

MeSH Headings have a number of Qualifiers associated with them to allow focus on items of interest. Thus, the MeSH term Cadmium/toxicity allows records to be retrieved related to the toxicity of Cadmium. There were 83 topical MeSH Qualifiers (in Pubmed) used for indexing and cataloging in conjunction with MeSH Heading descriptors when this concept was developed. All 83 were examined in more or less detail for applicability to identifying foundational causes of disease. Four were selected (after extensive validation) as producing highly relevant results when used in isolation: adverse effects, toxicity, pathogenicity, poisoning. A few limited combinations of the remaining MeSH Qualifiers were examined for the streamlined approach, but none were deemed to have sufficient relevance. All MeSH terms that contained at least one of these Qualifiers were extracted, and the related records examined for potential foundational causes. While this MeSH Qualifier linking approach was developed for, and applied to, identifying existing foundational causes, it was easily modified for identifying existing treatments and biomarkers, and could be further modified for identifying mechanisms, etc.

6B2b2. MeSH Headings

MeSH Headings related relatively unambiguously to foundational causes were identified two ways. First, results from past studies were examined, especially [Kostoff, Porter, Buchtel, 2018; Kostoff and Patel, 2015], and relevant MeSH Headings were extracted. Second, a few of the most unambiguous MeSH terms identified from past studies were entered into Pubmed as query terms, and all the MeSH terms in the resultant retrieval (i.e., those that co-occurred with the entry MeSH terms) were examined for relevance. The final list of relevant MeSH terms was intersected with the total list of MeSH terms in the retrieved database, and the resulting records were examined for potential PN/PAD foundational causes.

Sample MeSH terms related relatively unambiguously to foundational causes included: "Drug-Related Side Effects AND Adverse Reactions"; Abnormalities, Drug Induced; Air Pollutants, Occupational;

Amphetamine Related Disorders; Carcinogens; Chemical Warfare Agents; Chemically-Induced Disorders, etc.

Again, while this focused MeSH Heading approach was developed for identifying foundational causes, it was adapted to identifying treatments, and could be readily adapted to identifying biomarkers, mechanisms, etc.

6B3. Identifying Existing PN/PAD Treatments

6B3a. Text-based Approach

6B3a1. Visual Inspection

The text-based approach had two components: a visual inspection component, and a linking term component. The parsed Abstract field, containing about 4,000,000 phrases, was used for both components. The visual inspection component involved reading the 30,000 highest frequency phrases, and selecting those phrases deemed to be candidate treatments. The Vantage Point (VP) software containing these phrases displays both the phrases and the Titles and Abstracts of the records in which they appear. This allows validation of each candidate treatment selected.

6B3a2. Linking Term

To identify candidate treatments in the lower frequency portion of the parsed Abstract field, a text-mining approach was necessary. Linking terms strongly associated with treatments were generated through visually inspecting many records containing treatments in the Titles, and identifying those terms that appeared frequently with the treatments. The remainder of the parsed Abstract field was searched with use of these linking terms. The additional candidate treatments were extracted from the retrieved phrases, and validated as treatments.

Some of the more useful linking terms identified included the following: treat*, therap*, prevent*, protect*, improv*, reduc*, attenuat*, ameliorat*, enhanc*, revers*, promot*, alleviat*, inhibit*, remov*, suppress*, mitigat*, restor*, lower*, preserv*, regenerat*, rescu*, slow*, neuroprotect*, neurorestorati*, decreas*, increas*, eliminat*.

Not all these terms are of equal value, or efficiency in identifying the desired text concepts. Some of these terms had higher efficiencies of identifying the PN/PAD treatment consequences of interest (PN/PAD characteristics) than others. Terms like prevent*, protect*, improv*, restor*, alleviat*, ameliorat*, mitigat*, etc, almost always were associated with treatments, and gave the desired PN/PAD characteristics and the direction in which they changed as a result of PN/PAD treatment. Terms like decreas*, increas*, reduc*, etc, could go either way. The former group of terms had the 'sense' of improvement, while the latter group of terms reflected change (positive or negative).

6B3b. MeSH-based Approach

6B3b1. MeSH Qualifiers

MeSH Headings have a number of Qualifiers associated with them to allow focus on items of interest. Thus, the MeSH term Cadmium/toxicity allows records to be retrieved related to the toxicity of Cadmium. There were 83 topical MeSH Qualifiers (in Pubmed) used for indexing and cataloging in

conjunction with MeSH Heading descriptors when this concept was developed. All 83 were examined in more or less detail for applicability to identifying treatments. For the initial Visual Inspection approach query, seven were selected (after extensive validation) as producing highly relevant results when used in isolation: diet therapy, drug therapy, prevention & control, radiotherapy, surgery, therapeutic use, therapy. A few limited combinations of the remaining MeSH Qualifiers were examined for the streamlined approach, but none were deemed to have sufficient relevance. All MeSH terms that contained at least one of these Qualifiers were extracted, and the related records examined for treatments.

6B3b2. MeSH Headings

MeSH Headings related relatively unambiguously to treatments were identified two ways. First, results from past studies were examined, especially [Kostoff, Porter, Buchtel, 2018; Kostoff and Patel, 2015], and relevant MeSH Headings were extracted. Second, a few of the most unambiguous MeSH terms identified from past studies were entered into Pubmed as query terms, and all the MeSH terms in the resultant retrieval (i.e., those that co-occurred with the entry MeSH terms) were examined for relevance. The final list of relevant MeSH terms was intersected with the total list of MeSH terms in the retrieved database, and the resulting records were examined for candidate PN/PAD treatments.

Sample MeSH terms related relatively unambiguously to treatments included Treatment Outcome, Neuroprotective Agents, Nootropic Agents, Plant Extracts, Phytotherapy, Dietary Supplements, Drugs, Chinese Herbal, etc.

6B4. Identifying Existing PN/PAD Characteristics

6B4a. Text-based Approach

6B4a1. Visual Inspection

The text-based approach had two components: a visual inspection component, and a linking term component. The parsed Abstract field, containing about 4,000,000 phrases, was used for both components. The visual inspection component involved reading the 30,000 highest frequency phrases, and selecting those phrases deemed to be candidate characteristics. The Vantage Point (VP) software containing these phrases displays both the phrases and the Titles and Abstracts of the records in which they appear. This allows validation of each candidate characteristic selected.

6B4a2. Linking Term

To identify candidate characteristics in the lower frequency portion of the parsed Abstract field, a text-mining approach was necessary. Linking terms strongly associated with characteristics were generated through visually inspecting many records containing characteristics in the Titles, and identifying those terms that appeared frequently with the characteristics. The remainder of the parsed Abstract field was searched with use of these linking terms. The additional candidate characteristics were extracted from the retrieved phrases, and validated as characteristics.

For the streamlined approach, the linking terms used for identifying treatments were selected as the linking terms to be used for identifying characteristics. These linking terms included: treat*, therap*, prevent*, protect*, improv*, reduc*, attenuat*, ameliorat*, enhanc*, revers*, promot*,

alleviat*, inhibit*, remov*, suppress*, mitigat*, restor*, lower*, preserv*, regenerat*, rescu*, slow*, neuroprotect*, neurorestorati*, decreas*, increas*, eliminat*.

6B4b. MeSH-based Approach

6B4b1. MeSH Qualifiers

MeSH Headings have a number of Qualifiers associated with them to allow focus on items of interest. Thus, the MeSH term Cadmium/toxicity allows records to be retrieved related to the toxicity of Cadmium. There were 83 topical MeSH Qualifiers (in Pubmed) used for indexing and cataloging in conjunction with MeSH Heading descriptors when this concept was developed. All 83 were examined in more or less detail for applicability to identifying characteristics. None were identified as being unambiguously related to characteristics, and this approach was not pursued further.

6B4b2. MeSH Headings

MeSH Headings related relatively unambiguously to characteristics were identified two ways. First, results from past studies were examined, especially [Kostoff, Porter, Buchtel, 2018; Kostoff and Patel, 2015], and relevant MeSH Headings were extracted. Second, a few of the most unambiguous MeSH terms identified from past studies were entered into Pubmed as query terms, and all the MeSH terms in the resultant retrieval (i.e., those that co-occurred with the entry MeSH terms) were examined for relevance. The only MeSH term related relatively unambiguously to characteristics was Biomarkers.

6B4c. Spinoff from Contributing Factor and Treatment Identification Approaches

Contributing factor or treatment records typically identify one or more characteristics that are impacted by the contributing factor(s) or treatment(s) in the record. In the present streamlined approach, most of the characteristics were identified during the validation process for a contributing factor or treatment. The records were read for validation, and any characteristics were then extracted from the record.

6B5. Identifying Potential PN/PAD Treatments

Existing treatments identified in the present monograph were deemed successful when they moved the values of characteristics in desired directions. Thus, if high oxidative stress or high inflammation reflected an undesired disease state, then one component of a successful treatment for this undesired disease state would be reduction of oxidative stress or reduction of inflammation. One of the outcomes of the present study was identification of myriad characteristics and the directions in which they changed as a result of successful treatments.

For Discovery (identification of potential PN/PAD treatments), this process is reversed. A query is formed consisting of critical characteristics and the directions in which they would be changed if successful treatments were applied. This query is then applied to the full Medline database excluding the PN/PAD literature. Chemicals/radiations/supplements etc, and other forms of potential PN/PAD treatments are identified that move these characteristics in desired directions, and they are viewed as candidate potential PN/PAD treatments. A validation is performed to insure these candidate potential PN/PAD treatments are not part of the core PN/PAD literature.

The number of terms in the query could range from one to many. The more terms in the query, the more restricted the retrievals would be in volume and focus. The fewer terms in the query, the greater the chances for radical discovery, but the larger the volume of retrieval to be evaluated for validation.

As an example, consider the above case of an undesired disease state, characterized by high oxidative stress and high inflammation. A query would be generated, consisting of "reduce oxidative stress AND "reduce inflammation". All treatments for any disease in Medline (with the exception of PN/PAD) that reduced oxidative stress and reduced inflammation would be retrieved. After much experimentation, it was found that queries consisting of combinations of two biomarkers (with desired directions of change) provided a good balance between content of discovery and volume of retrieval.

The detailed methodology that was used in the present study is described in Appendix 6-1, and in the broader context of ***treatment re-purposing*** in [Kostoff, 2018].

6B6. Identifying Potential PN/PAD Contributing Factors

Potential PN/PAD contributing factors were not identified in the present study because of time and resource limitations. However, the conceptual approach is the same as that for identifying potential PN/PAD treatments, with the exception that the directions in which characteristics changes are desired are reversed. In the example provided in section 6B5 for treatments, the query for identifying potential contributing factors would be "increase oxidative stress" AND "increase inflammation". All contributing factors for any disease in Medline (with the exception of PN/PAD) that increased oxidative stress and increased inflammation would be retrieved.

6B7. Identifying Potential PN/PAD Characteristics

Potential PN/PAD characteristics were not identified in the present study because of time and resource limitations. If potential PN/PAD characteristics were desired, the identification concept would be to identify patterns of PN/PAD characteristics that tend to co-occur frequently in the PN/PAD literature, then use these patterns as a search query in the non-PN/PAD literature. New patterns may be identified in the non-PN/PAD literature consisting of the search query pattern plus additional characteristics not in the PN/PAD literature. These additional characteristics would then be candidates for discovery as new PN/PAD characteristics that not have been identified previously.

For example, IL-1 and IL-6 and TNF-alpha and NF-KappaB tend to co-occur in many PN/PAD articles relating to inflammation. These four terms would be combined as a query for the non-AD literature: "**IL-1** AND **IL-6** AND **TNF-alpha** AND **NF-KappaB**". Any records retrieved would be examined for additional characteristics, and these additional characteristics would be validated if they did not occur in the PN/PAD literature.

Myriad other patterns are possible. For example, existing PN/PAD treatments and existing PN/PAD causes move PN/PAD characteristics in known directions. Non-PN/PAD literatures could be searched for characteristics impacted by these known PN/PAD treatments and PN/PAD causes, and not contained in the core PN/PAD literature. Combinations of these PN/PAD treatments and PN/PAD causes could be used to increase the likelihood that any new characteristics identified would have higher relevance to PN/PAD.

As a specific example, consider the following query that was demonstrated in the Alzheimer's Disease (AD) study [Kostoff, Porter, Buchtel, 2018]: (high-fat-diet* NEAR/5 (increas* OR decreas*) AND chitosan NEAR/5 (increas* OR decreas*)) NOT alzheimer*. This will retrieve all records reflecting an increase or decrease of characteristic values (in the non-AD literature) due to the presence of the existing AD cause "high-fat-diet" and the existing AD treatment "chitosan". Applying this query to the Medline database leads to the identification of a potential AD characteristic "mup17" (major urinary protein 17) [Wang, Zhang, Wang et al, 2017]. This potential AD characteristic is not found in the AD literature, but it is altered in one direction by an existing AD cause, and is altered in the opposing direction by an existing AD treatment. So, it might be a valuable characteristic for AD researchers to track.

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APPENDIX 5 – FOUNDATIONAL CAUSES OF AD

2-7C. Specific Foundational Causes of AD

Table 2-7C shows the AD potential foundational causes in this detailed taxonomic structure. There are four columns listed. The first column on the left (CAT) is the foundational cause category as shown in Table 2-7A. The next column is the foundational cause. To keep the volume of results manageable, in some cases only the cause in aggregate was shown, rather than listing all the members (e.g., vegetables). The third column is the effect(s) produced by the foundational cause, and the entry tags are those listed in Table 2-7B. The fourth column contains relevant references that confirm the foundational cause.

In most cases, there were multiple papers linking each foundational cause listed either directly to AD or indirectly to one or more surrogate endpoints. Referencing every single relevant paper for every detailed foundational cause would have produced an overly voluminous unreadable table and write-up. In order to balance comprehensiveness with readability, multiple compromises were made.

First, one or two representative papers for each foundational cause were selected and referenced. Second, foundational causes that had relatively minor differences were aggregated. Some were listed separately under a categorical heading, and others were subsumed within the heading. Third, the effects/impacts of the foundational causes were extracted from at least the papers referenced, and sometimes from other relevant papers that were not selected for referencing. Thus, the effects/impacts shown for any potential cause should be viewed as a "floor" of all potential effects, not a "ceiling".

It should also be noted that all the effects/impacts were derived from papers whose central theme was AD/dementia, because of the criteria used to extract these records from Medline. So, a foundational cause that, e.g., "damaged mitochondria" (A6) did so within the overall context of relating to AD or dementia. If the four different levels shown, and the items contained in each level, are viewed as potential "pathways" to AD, then conventional wisdom implies that the more pathways impacted by a potential contributing factor, the greater likelihood that factor would be an important "cause" of AD. However, not only are the numbers of pathways impacted important, but the strength of the contributing factor's impact on each pathway is important. This strength of impact is not shown in the table, reflecting its ambiguity in the literature.

The foundational causes identified are at different levels of importance to AD, and are at different levels of verification/validation. In the Medline literature examined, some foundational causes were identified through:

1) in vitro cell or tissue tests;

2) animal experiments;

3) epidemiological studies;

4) individual case studies; and,

5) trials with large numbers of subjects.

Conventional wisdom implies that those foundational causes associated with large numbers of papers published and large numbers of test subjects would have greater credibility. However, as shown in [2-3], there may be (many) important foundational causes being withheld from the literature deliberately, so numbers of papers is not a definitive metric for credibility.

Table 2-7C - Foundational Causes of AD

(adapted from reference [1])

CAT	CAUSE	EFFECTS	REF
I	**LIFESTYLE**		
I-A	**DIET**		
I-A1	EXCESSES		
	High Fat Diet -saturated fat -dairy fat -trans-unsaturated fat -hydrogenated fat -omega-6 PUFAs -n-6/n-3 ratio -maternal high fat diet	A2, B1, B2, C1, C3, D1, D4, D5	[3-12]
	Diabetogenic diet	B2	[13]
	High calorie diet	A1, B1, B12, C3, D1, D5	[14-16]
	High salt diet	B2, C3, D1	[17]
	High carbohydrate diet -refined carbohydrates -sugars (fructose/sucrose/glucose/D-galactose) -gluten -high glycemic index diet	A1, A3, A4, A7, B2, B4, B11, B12, B13, C1, C3, D1, D2	[18-25]
	High advanced glycation end products diet -high temperature food heating -food irradiation -high glucose -high nutrient-bound AGEs -animal foods high in fat and protein	A6, A7, B1, B2, B3, C1, C3, D1, D2	[26-31]
	High cholesterol diet	A1, A4	[32]
	High iron diet -high red meat -high processed meat	A1, C3, D1	[33-35]
	High meat diet	D1	[36]
	High arachidonic acid	B1	[37]
	High methionine diet	A1, A2, A7, B1, B8, B2, C1, C3	[38-40]
	High copper diet	C3, D1	[35, 41]
	High zinc	A3, A7, B1, B2	[42-43]
	High pickle diet	D1	[44]
	High unfermented soy	D1	[45]
I-A2	DEFICIENCIES		

	Vitamin B deficiency -myriad B-Vitamin deficiency -B2/B6/B12 deficiency -folate/folic acid deficiency -thiamine deficiency	A3, A4, A6, A7, B1, B2, C1, C3	[46-49]
	Vitamin C deficiency	A7, C2	[50]
	Vitamin D deficiency	A1, A4, A6, B1, B2, B5, B8, C3, D1	[51-52]
	Vitamin E deficiency	D1	[53]
	Vitamin K deficiency -fluindone	C3	[54]
	Potassium deficiency	A1, A3, A7, B1, B2, C3	[55-56]
	Iron deficiency	C3	[57]
	Zinc deficiency	A3, C3, D1	[58]
	Magnesium deficiency	C3	[59]
	Calcium deficiency	A3, A7	[60]
	Selenium deficiency	B2	[61]
	Starvation	B2	[62]
	Dehydration	B5, D1, D2, D5	[63]
	Malnutrition	D1	[64]
	Early life nutrient restriction	B2, D1	[65]
	Glucose deprivation	A3, B1, B2	[66]
	Glutathione depletion	A1, A2, A4	[67]
	Linoleic acid deficiency	A4, D1	[68]
	Low docosahexaenoic acid	A3	[53]
	Low tryptophan diet	B2	[69]
	Nondrinkers	C3, D1	[70]
	Low cocoa	A1, A7, C3	[71]
	Low coffee	C3, D1	[72]
	Low flavonoids/flavanols: acacetin, aminogenistein, apigenin, kaempferol, 7,8-Dihydroxyflavone, anthocyanins, atriplex laciniata L, blueberries, Curcumin, cyanidin, datiscetin, delphinidin, EGCG, epicatechin, Epimedium brevicornum, fisetin, genistein, Ginkgo, glycitein, icariin, isoscutellarein 7-O-[6'''-O-acetyl-beta-D-allopyranosyl-(12)]-beta-D-glucopyranoside, isovitexin, morin, myricetin, Nobiletin, pelargonidin, phloridzin, rutin, salvigenin, Scutellaria baicalensis Georgi, Sideritis flavonoids, vitexin, xanthomicrol, luteolin, morin, PD98059, quercetin, taxifolin, β-naphthoflavone	A1, A7, B2, C3, D1	[71, 73-74]

	Low fruit: **low**: blackberries, blueberries, strawberries, raspberries, cherries, oranges, plums, prunes, red grapes, pomegranates, date palm fruits	A7, B2, B3, B13, C1, C3, D1	[21, 75-76]
	Low vegetables -cruciferous -dark and green leafy	A7, B13, C3, D1	[8]
	Low fatty fish	B2, C3, D1	[77]
I-A3	FOOD ADDITIVES/POLLUTANTS		
	Industrialized/preserved food	D1	[78]
	Monosodium glutamate	A2, A3, B2, B9	[79]
	Menadione	A3, A7	[80]
	Cysteine	A7	[81]
	Diacetyl	A2, B2	[82]
I-B	**ACTIVITY**		
I-B1	SEDENTARY LIFESTYLE		
	Physical inactivity/low daily gardening, walking	A6, A7, D1	[83-84]
	Chronic immobilization stress	A4, B1, B2, B9, C3	[85]
	Cognitive inactivity	D1	[86]
	Lack of exercise	D1, D2	[23]
	Low cardiovascular fitness	D1	[87]
I-B2	SLEEP		
	Sleep deprivation	C3, D1	[20, 88]
	Circadian disruption	C1, C3	[89-90]
I-C	**SUBSTANCE ABUSE**		
I-C1	RECREATIONAL DRUGS		
	Amphetamine	C3	[91]
	3,4-Methylenedioxyamphetamine; MDMA; Ecstacy	A2, A7, B1, C1, C3	[92]
	Cocaine/opiates	A2, A4	[93-94]
	Phencyclidine	C3	[95]
I-C2	SMOKING		
	Tobacco smoke	A4	[96]
	Ethanol/excess alcohol	A7, B9, C1, C3, D1	[97]
II	**IATROGENIC**		
II-A	**DRUGS**		
II-A1	ANTI-NEOPLASTIC AGENTS		
	Chemotherapy	A2, A4, B9	[98]
	Chemical castration	C3	[99]
	Camptothecin	A2, A3	[100]
	Epoxomicin	A3, A6	[101]
	Staurosporine/Etoposide	A3, A4	[102-103]
	Methylmethane sulfonate	A5	[104]
	Paclitaxel/Doxorubicin	A3, A4, B1	[105]
	Doxycyclin	B2	[106]

	Cyclophosphamide/cytophosphane	A2, A7	[107]
	Letrozole	B9, C1	[108]
	Methotrexate	B9, C1, C3	[109]
	Choline mustard Az/Nitrogen mustard	B9, C1	[110]
	Anastrozole	B2, B9	[111]
	d,l-buthionine-S,R-sulfoximine/BSO	A3, A6, A7, B14	[112]
	Fostriecin/Fos	B1	[113]
	carbobenzoxy-Leu-Leu-leucinal/MG132	A2, A4	[114]
	Streptozocin	B14, D1	[115]
II-A2	ANTI-INFECTIVE AGENTS		
	Chloroquine(CQ); CQ; lysosomotropic agent	B2	[116]
	Ionomycin	A6, B2	[117]
II-A3	ANTI-INFLAMMATORY AGENTS		
	colchicine	A1, A4, C1, D1	[118]
II-A4	CARDIOVASCULAR AGENTS		
	isoproterenol	B1, C1	[119]
	atropine	B2	[120]
	D-ribose	A3, B1, B3	[121]
	Muscarinic receptor antagonists	C1, C3	[122]
II-A5	CENTRAL NERVOUS SYSTEM AGENTS		
II-A5a	Analgesics and Pain Relievers		
	Anesthetics/Opiods -acetaminophen -barbital -barbitone -desflurane -dexmedetomidine -diethylbarbituric acid -diethylmalonyl urea -enflurane -halothane -isoflurane -ketamine -medinal -morphine -nitrous oxide -pentobarbital -propofol -psychotropic drugs -sevoflurane -sodium diethylbarbiturate -veronal	A2, A3, A4, A6, B1, B2, B9, C1, C3, D1	[123-129]
II-A5b	Movement Stabilizers		

	Anticholinergic medications -doxepin -chlorpheniramine -oxybutynin -trihexyphenidyl -propiverine -L-DOPA/dopamine	A3, A7, B1, C3, D1	[130-132]
II-A5C	Depressants/Anti-Depressants and Stimulants		
	selective serotonin re-uptake inhibitors	D1	[133]
	benzodiazepine	D1	[134]
	dizocilpine	C1, C3	[135]
	3-quinuclidinyl benzilate	C3	[136]
II-A5d	Mood Stabilizers		
	-clozapine -methyllycaconitine -dihydro-beta-erythrodine	C1, C3	[137]
	anisomycin	A7, B2	[138]
II-A6	IMMUNE SYSTEM AGENTS		
II-A6a	Immunosuppressive Agents/ Immunosuppression		
	Cyclosporin	B1, C1	[139]
II-A6b	Immunostimulation Agents		
	polyinosinic:polycytidylic acid	B2, C3	[140]
II-A7	Hematologic Agents		
II-A7b	Anti-Coagulants		
	Sulfated glycosaminoglycans -heparin/heparan sulfate -dextran sulfate -pentosan polysulfate -chondroitin sulfate -dermatan sulfate	B1	[141]
II-A7c	Other		
	mitochondrial toxins -1-methyl-4-phenyl-1,2,3,6- tetrahydropyridine/MPTP	A1, A3, A6, A7	[142]
II-A8	Steroids/Hormones		
	Corticosteroids -methylprednisolone -dexamethasone	A1, A3, A4, B1, B5	[143-145]
	Anabolic androgenic steroids -nandrolone -stanozolol	B8, B9, C1, C3	[146]
	Corticosterone	B1, B2, C3	[147]
	Wortmannin	A7, B1	[148]

	17beta-trenbolone	A3, A4, B2	[149]
	Salmon calcitonin	B2	[150]
	Human chorionic gonadotropin	B2	[151-152]
	Corticotrophin releasing factor	B2	[153]
	Sex steroid hormones -transient testosterone treatment -flutamide	B2	[154]
	U18666A	A3, A7, B2	[155]
	Allopregnanolone	B9, C1, C3	[156]
	Medroxy-progesterone acetate	C3, D1	[157]
	Androgen deprivation therapy	D1	[158]
	Postmenopausal hormone therapy	C3	[159]
	Testosterone depletion	A1, D1, D2	[160]
	Leptin deficiency	B1	[161]
	Prenatal sex hormone exposure	D1	[162]
II-A9	ANTI-HYPERTENSIVE AGENTS		
	ACE inhibitor	D1	[163]
	ICI 118,551/Selective beta2AR antagonist	B1, B2, C3	[164]
	Telmisartan/Olmesartan	B2	[165]
	Mecamylamine	C3	[166]
II-A10	GASTROINTESTINAL AGENTS		
	Thiorphan/Phosphoramidon	B2	[167]
	Proton pump inhibitors -omeprazole -pantoprazole -lansoprazole -esomeprazole -rabeprazole	B2, D1	[168-169]
II-A13	ANTI-BONE-LOSS AGENTS		
	PGE2	B2	[170]
II-A14	ANTI-DIABETIC AGENTS		
	Intralipid and insulin	B2	[171]
	Metformin	B2	[172]
II-A16	ANTI-ALLERGIC AGENTS		
	Anticholinergics -first-generation antihistamines -tricyclic antidepressants -bladder antimuscarinics	D1	[173]
II-A18	ANTI-THYROID AGENTS		
	Propythiouracyl	A1, B1, B2, B5, B8, C1	[174]
II-A19	Other		
	Carbachol	B8, B14	[175]
	MDL72974/Mofegiline	A3, A7	[176]
	Pilocarpine	A3, B1, B2	[177]

	Clenbuterol hydrochloride	B2	[178]
	Semagacestat	C3	[179]
II-B	**RADIOTHERAPY**		
	Head radiotherapy	C3, D1	[180-181]
II-C	**SURGERY/ INVASIVE TREATMENTS**		
II-C1	TRANSPLANTATION		
	Liver transplant	B2, C3	[182]
II-C2	CARDIOVASCULAR		
	Cardiac surgery/bypass	A1, B1, B2, C3	[183-185]
II-C5	KIDNEY/UROLOGIC		
	Dialysis	C1, C3	[186-187]
	Gonadectomy	B2	[188]
II-C7	DENTAL/ORAL/NOSE/EAR		
	Olfactory bulbectomy	A4, A6, A7, B2, C1	[189-190]
	Occlusal disharmony	B2	[191]
II-C8	GYNECOLOGIC		
	Hysterectomy/oophorectomy	C3	[192]
	Premature surgical menopause/Premature ovarian failure	C3	[193]
II-C17	OTHER		
	Axotomy	A3, A7	[194]
	Cerebral artery occlusion	A3, A4, A7, B8, C1, C3	[195-198]
	Intermittent hypoxia/ischemia	A3, A4, A7, B2, B12, C1, C3	[199-202]
	Brain embolism	A4, B1, B2, C1, C3	[203-204]
	Aortic coarctation	A1, B2	[205]
	Forebrain lesions	C1, C3	[206-207]
	Adrenalectomy	B2	[208]
	Pituitary hormone injections with Abeta	B2	[209]
	Abdominal surgery	B2, C3	[210]
III	**BIOTOXIC AGENTS**		
III-A	**MYCOTOXINS**		
	Mycotoxins -ochratoxin A/OTA -Fumonisin B1/FB1 -macrocyclic trichothecenes	A2, A3, A4, A7, B1, C1, C3, D1	[211-214]
	3-nitropropionic acid	A6	[215]
III-B	**EXOTOXINS**		
	Excitotoxins -kainic acid/ kainate -quisqualic acid -ibotenic acid -domoic acid -quinolinic acid/quinolinate	A1, A2, A3, A4, B9, C1, C2, C3,	[216-220]
	Phosphatase inhibitor	B1	[221]

	-okadaic acid		
	Excitatory amino acids	D1	[222]
	Malonate	B9	[223]
	Annonaceaeous acetogenins	A2, D1	[224]
	Cyanobacteria -beta-N-methylamino-L-alanine/BMAA -saxitoxin -anatoxin-a -blue-green algae -microcystin	A2, B1, B2, B14	[225-228]
	Diphtheria toxin	B2	[229]
	Pseudomonas aeruginosa exotoxin Y	B1, B12	[230]
	Saporin -192 IgG-saporin -p75-saporin	B1, B2, B13, C3	[231-233]
	Cycad plant -cycasin/methylazoxymethanol	A2, A4, A5	[234]
	Glutamate/Glutamine synthetase	A2, A3, A4, A6, B2	[235-237]
	Mitochondrial inhibitors -rotenone -3-NPA -antimycin -KCN -oligomycin	A6	[238]
III-C	**BACTERIA/FUNGI/PARASITES**		
	Bacteria/bacterial infections -bacterial endotoxins -bacterial lipopolysaccharide -gram-negative bacterium -spirochetes -Chlamydophyla pneumoniae -Helicobacter pylori -Escherichia coli -Treponema pallidum -Tannerella forsythia -Treponema denticola -T. socranskii -T. pectinovorum -T. medium -T. amylovorum -T. maltophilum -Fusobacterium nucleatum -Prevotella intermedia -Chlamydia pneumoniae -Porphyromonas gingivalis -propionibacterium acnes	A1, A4, A7, B1, B2, B3, C3, D1	[239-253]

	-Treponemas -T. lecithinolyticum -Borrelia burgdorferi Fungi/fungal infection -Cryptococcus -Coccidioides -Aspergillus -Histoplasma -Blastomyces -C. famata -C. parapsilosis -C. glabrata -C. krusei -Candida albicans -Candida ortholopsis -Candida tropicalis -Cladosporium -Malassezia globosa -Malassezia restricta -Neosartorya hiratsukae -Phoma -Sacharomyces cerevisae -Sclerotinia borealis Parasites -Trypanosoma brucei rhodesiense -Trypanosoma brucei gambiense -Acanthamoeba -Balamuthia mandrillaris -Toxoplasma gondii -Taenia solium -Toxocara canis -T. cati -Toxocara ova -Leishmania amazonensis		
III-D	**VIRUSES**		
	Viruses/Viral infections/Virulence factors Bornaviridae -Mammalian 1 bornavirus Bunyaviridae -Hantavirus -La Crosse encephalitis virus Coronaviridae -Human coronavirus OC43 -Murine hepatitis virus Flaviviridae -Hepatitis C virus	A1, A3, A4, B1, B2, C3, D1	[254-260]

	-Japanese encephalitis virus -Murray Valley encephalitis virus -St. Louis encephalitis virus -West Nile virus Hepadnaviridae -Hepatitis B virus Herpesviridae -Cytomegalovirus -Epstein-Barr virus -Herpes simplex virus 1 -Human herpesvirus 6 Orthomyxoviridae -Influenza A virus (H1N1) -Influenza A virus (H3N2) -Influenza A virus (H5N1) Paramyxoviridae -Hendra virus -Measles virus Picornaviridae -Enterovirus 71 -Theiler's murine encephalomyelitis virus Polyomaviridae -Simian 40 virus large T antigen Retroviridae -Human immunodeficiency virus 1 -Human T-cell leukemia virus -Moloney murine leukemia virus Rhabdoviridae -Chandipura virus Togaviridae -Chikungunya virus -Eastern equine encephalitis virus -Venezuelan equine encephalitis virus		
III-E	**OTHER**		
	Abeta -amyloid precursor protein -C31 -CT105 -Curli fibrils	A1, A2, A3, A4, A6, B2, B8, B14, C1, C3	[261-271]
	Homocysteine/3-Mercaptopropionic Acid	B8, B12, C1	[272-273]
	Lipopolysaccharide	A7, B3, C1	[274]
	Prions/Prion protein fragment	A2, A3, B14	[275-277]
	Cytokines -CXCL10 -IL-1 beta -IL-10	A1, A2, A3, A4, B1, B2, B9, C1, C3	[278-288]

	-interferon-alpha -interferon-gamma -interleukin-6 -interleukin-18 -interleukin-8 -TNF-alpha		
	Lipoperoxydation proteins -advanced lipoperoxydation products -oxidized low density lipoprotein	A1, A2, A3	[289-290]
	Trophic factor withdrawal	A3, A4, B2	[291-293]
	Amylin	A1, A2, A4, A6, A7	[294]
	Lysophosphatidic acid	B2	[295]
	S100B	A1, B1, B2	[296]
	3-hydroxykynurenine/3-hydroxyanthranilic acid	A4, A7, B2	[297]
	Abscisic acid	A1	[298]
	Phorbol myristate acetate	A1	[298]
	Acid phosphatase	D1	[299]
	2-deoxy-D-glucose	B2	[300]
	3-methylindole/Skatole	B10	[301]
	alpha-amino-3-hydrozy-5-methyl-4-isoxazole propionic acid/AMPA	A2	[302]
	Asymmetric dimethylarginine	A2, A7, B2, C3	[303-304]
	Dolichyl phosphate	B12	[305]
	N-(2-chloroethyl)-N-ethyl-bromo-benzylamine/dsp4	A1, A3, A4, B2, B13, C1	[306]
	Galanin	C1, C3	[307]
	GW4869/hydrochloride hydrate	B2	[308]
	Cottonseed	B1, B2	[309]
	Homocysteic acid/Homocysteate	A3, A7	[310]
	Isoprostane	B2	[311]
	Lysophosphatidylcholine	A2, A3, A7, B2	[312]
	Saturated non-esterified fatty acids	B2	[313]
	Palmitic acid	A3, C3	[314]
	Oncostatin M	A2, B11	[315]
	S100A9	A1, B2, C3	[316]
	Salsolinol	A2, A3	[317]
	Sulfatide	A3	[318]
	Brefeldin A	A3, A6, A7	[319]
	Thapsigargin	A3, A6, A7	[319]
	GF-109203X	B1	[320]
	Isopropyl-1-beta-D-thiogalactopyranoside	A3, A6, B1	[321]
	C2-ceramide	A3, A7	[322]
	dl-threo-1-phenyl-2-decanoylamino-3-morpholino-1-propanol/PDMP	B2	[323]

	(1S,2R-d-erythro-2-N-myristoylamino)-1-phenyl-1-propanol/DMAPP	B2	[323]
	alpha7 nAChR subunit alpha7(1-208)	A1, B2, C3	[324]
	Adenosine triphosphate/ATP	B1	[325]
	Recombinant BiP/GRP78	B2	[326]
	Bradykinin	B1, B14	[327]
	CD40/CD40L	B2	[328]
	Collagen	B2	[329]
	Cyclic dipeptides	A3	[330]
	D-serine	A7	[331]
	Elastase	A7, B1	[332]
	4-Hydroxyhexenal/HHE	A3, B11, B13	[333]
	High-mobility group box-1/HMGB1	C3	[334]
	Exogenous amyloidogenic proteins -casein -fibroin -sericin -actin -islet amyloid polypeptide	B2	[335]
	Leukotrienes -Leukotriene B4/LTB4 -Leukotriene D4/LTD4	A1, B2, C1	[336-337]
	Myostatin precursor protein	B2	[338]
	N-acetylcholinesterase	A3, B1	[339]
	Secreted phospholipase A2-IIA/sPLA2-IIA	A1	[340]
	Spermine	A2	[341]
	Xanthine oxidase	A3, A7	[342]
	3-hydroxykynurenine/3-HK	A2, A3, A6	[343]
	Mitochondrial lysates	A1	[344]
	Phytohemagglutinin	A3, B14	[345]
	Angiotensin II	B1, B2, C3	[346]
	3beta-hydroxy-5-oxo-5,6-secocholestan-6-al/ ChSeco	A2, A3, A7, B2	[347]
	Cholesterol oxidation products/oxysterols -27-hydroxycholesterol/27-OHC -24-OH -7beta-hydroxycholesterol -7-ketocholesterol -5,6-alpha cholesterol epoxide -5,6-beta cholesterol epoxide -cholesterol triol -lathosterol -beta cholesterol epoxide -cholesterol triol	A1, A2, A7	[348-349]
	Calyculin A	A2, A7, B1	[350]

	Chromogranin A	A1	[351]
	Forskolin	B1	[352]
	N-methyl-D-aspartate	A3, B9	[353]
	PGJ2	A1, A3, B1	[354-355]
	Quisqualate	A3, B9, C2	[356]
	Tunicamycin	A3, B14	[357]
	2-chloro-2'-deoxyadenosine/2-CDA/ cladribine	B2, C3	[358]
	N-acetylglucosamine	A2, B8, B9	[359]
	Cholinesterase -acetylcholinesterase -butyrylcholinesterase	B2	[360]
	Glycogen synthase kinase 3-beta/GSK3beta	B1	[361]
	HMG-CoA reductase	D1	[362]
	Pam(3)CSK(4)	A1	[363]
	Superoxide dismutase deficiency	A1, A7, B1, B2, B3, C1	[364]
IV	**OCCUPATIONAL/ENVIRONMENTAL EXPOSURES**		
IV-A	**CHEMICALS/MATERIALS**		
IV-A1	INDUSTRIAL/HOUSEHOLD CHEMICALS/MATERIALS		
IV-A1a	Hydrocarbons		
	20-methylcholanthrene/methylcholanthrene	A1	[365]
IV-A1b	Solvents		
	Petroleum-based solvents -Mineral turpentine -Diesel fuel -Fuel oil -Kerosene	D1	[366]
	Chlorinated solvents -Trichloroethylene -Perchlorethylene -Trichloroethane -Dichloromethane -Benzene	C3	[367]
	Dimethyl sulfoxide/DMSO	B1	[368]
	Organic solvents -Benzene -Toluene -Phenols -Alcohols -Ketones -Methylmethacrylate	D1	[369-370]
IV-A1c	Chemical Compounds		
	Neurotoxins	A3, A7	[371-372]

	-6-hydroxydopamine/6-OHDA -5,6-dihydroxytryptamine/5,6-DHT -5,7-dihydroxytryptamine/5,7-DHT		
	Type-2 Alkenes/Reactive aldehydes -Acrolein -4-Hydroxynonenal/HNE -Acrylamide -Methyl glyoxal	A2, A3, A4, A7, B1, B2, B3, B8	[373-378]
	Nitrosamine/N-nitrosodiethylamine	A3, A4, B4, C3	[379]
	Adenosine, 3', 5'-cyclic monophosphate/ cAMP	B2	[380]
	Carbon tetrachloride	A1, A4, A7, B4, B13	[381]
	Chemical warfare agents/nerve agents -organophosphates -soman -sarin -ethyl S-2-di-isopropylaminoethyl-phosphonothiolate -VX -tabun	C1, C3	[382]
	Cyanide -Potassium cyanide -Sodium cyanide	A3, A7	[383-385]
	Formaldehyde	B1, C1	[386]
	Hydrogen Peroxide/H2O2	A2, A3, A6, A7	[387]
	Lipophilic chemicals -persistent organic pollutants -bisphenol A -phthalates -low molecular weight hydrocarbons -polynuclear aromatic hydrocarbons -endocrine disruptors	C3, D1	[388]
	Sulfur dioxide/ SO2	A2, B8, C3	[389]
	Phthalates -Di-(2-ethylhexyl)-phthalate/DEHP -mono-2-ethylhexyl phthalate/MEHP -DEHP metabolites	B1, B4, B14, C3	[390]
	Brominated flame retardants -hexabromocyclo-dodecane/HBCD -tetrabromobisphenol-Al/TBBPA -decabromodiphenyl ether/DBDE -polybrominated diphenyl ethers/PBDEs	A2, A3, A6, A7, B2	[391-392]
	Ammonia	A1, B2, B8	[393-394]
	Hypochlorous acid/HOCl	A2, A6, B13	[395-396]
	Methanol	A3, B1, C1	[397]

	Peroxynitrite	B1	[398]
	Sodium azide	A3, B1, B2	[399]
	Acetaldehyde	A3, A7	[400]
	3-Bromopyruvate	B13, C3	[401]
	Vehicular emission oxides -nitrogen dioxide/NO2 -carbon monoxide/CO	C3, D1	[402]
	Sodium fluoride	C1, C3	[403
	Membrane-mimicking detergents -sodium dodecyl sulfate -lithium dodecyl sulfate	B2	[404-405]
	Nitric oxide donors -sodium nitroprusside -DETA NONOate	B1	[406-407]
	Amorphous aluminosilicates	B2	[408]
	Sodium nitrite	A3, A4, B1, B2, B9, B11, C1	[409]
	Tert-butyl hydroperoxide/t-BHP	A3, A7	[410]
	Alloxan	B1, B2	[411]
	Ammonium chloride	A4, A6	[412]
	Anionic dyes -Congo Red -Thiazine Red -Thioflavin S	B1	[413]
	Aroclor 1254	A3	[414]
	Cobalt chloride	A2, A3, A6, A7, C1, C3	[415]
	Magnesium chloride	B2	[416]
	2,2'-azobis(2-methylpropionamidine) dihydrochloride/AAPH	A7	[417]
	Methylglyoxal/Glyoxal	A1, A2, A7, B12	[378, 418]
	Disuccinimidyl suberate	B2	[419]
	Naphthazarin/5,8-dihydroxy-1,4-naphthoquinone/5,8-dihydroxy-1,4-naphthalenedione	A7	[420]
	Pyrithiamine	B1, B2, C1	[421]
	Pyrogallol	A3, A7	[422]
	Glyceraldehyde-3-phosphate/GAPDH	A3, A6, B2	[423]
IV-A1d	Other		
	Ethylcholine mustard aziridinium ion/ AF64A	B8, C1	[424]
	1-methyl-4-phenylpyridinium ion	A2, A3, A6, A7	[425]
	2,2'-dithiodipyridine	B14	[426]
	Aftin-4	A7, B2, B8, C3	[427]
	Kaolin	B2	[428]
	Ozone	A3, A7, C1, C3	[429]
	2;3;7;8-tetrachlorodibenzo-p-dioxin	A2, D1	[430-431]

IV-A2	AGRICULTURAL CHEMICALS		
	Pesticides/Insecticides/Herbicides/Fungicides -Organochlorine Pesticides -Organophosphate Pesticides -2,4,5-trichlorophenoxyacetic acid -2,4-Dichlorophenoxyacetic Acid -Agent Orange -Aldrin -Alkylphenolpolyethoxylates -APEOs -Arsenic -Beta-hexachlorocyclohexane/beta-HCH -Bipyridyles -Carbamates -Carbofuran -Chlorfenvinphos -Chlorpyrifos/CPF -Cycloheximide -Cypermethrin -Deltamethrin -Dichlorodiphenyldichloroethylene/DDE -Dichlorodiphenyltrichloroethane/DDT -Dichlorodiphenyldichloroethane/DDD -Dieldrin -Dimethyl parathion -Endosulfan -Famoxadone -Fenamidone -Glyphosate -Hexachlorobenzene -Hexachlorocyclohexane/HCH -Imidacloprid -Lindane -Maneb -Methamidophos -Methyl parathion -Neonicotinoids -Nonylphenol -Octylphenol -Paraquat -Parathion -Pyraclostrobin -Pyrethroids -Trans-nonachlor -Trichlorfon/TCF -Trifloxystrobin	A1, A2, A3, A5, A6, A7, B1, B2, B11, B14, C1, C3, D1,	[391, 431-443]

IV-A3	MATERIALS		
IV-A3a	Heavy Metals		
	Heavy Metals -aluminum -arsenic -cadmium -calcium/Ca2/CaCl -calcium ionophore/A-23187/calcimycin -cobalt -copper -iron -lead -manganese -mercury -methylmercury -selenium -tin -zinc	A1, A2, A3, A4, A6, A7, B1, B2, B14, D1	[391, 444-455]
IV-A3b	Particulates		
	Air pollution -fine/ultrafine particles -inhalable dust -surgical smoke	A1, A4, A7, B1, B2, D1	[456-458]
IV-A3c	Nanotechnology		
	Nanoparticles -iron -titanium dioxide -CdSe quantum dots -diesel exhaust -alumina -manganese oxide -copper -silica/silicon dioxide -zinc oxide -silver -nickel	A1, A2, A3, A4, A7, B2, B8, B12; B14	[459-462]
IV-B	Physical/Mechanical		
IV-B1	Electromagnetic Radiation		
IV-B1a	Ionizing		
	Gamma radiation -dental X-ray -gamma rays	A3, B1	[463-464]
	Particle radiation -56Fe-particle radiation -cosmic radiation -HZE particle radiation	B2, B8, B9, B12, C3	[465-466]

	Radionuclide pollutants -uranium -cesium -cobalt -radon	A7, C1, C3, D1	[467-468]
IV-B1b	Non-Ionizing		
IV-B1b1	Non-Visible		
	Electromagnetic fields -extremely low frequency/ELF-EMF -900 MHz/RFEMR -electromagnetic pulse/EMP -electroconvulsive shock/ECS -UV irradiation	B1, B2, B8, B9, C1, C3, D1	469-473]
IV-B1b2	Visible		
	photolysis of 1-(2-nitrophenyl)ethyl sulfate	B2	[474]
IV-B2	SOUND		
	Noise -chronic noise exposure -short-lasting impulse noise -ultrasound sonication	A1, A4, B2, B3, D1	[475-477]
IV-B3	TEMPERATURE; HEAT/COLD		
	Heat stress -heat shock -heating -hyperthermia	A6, A7, B1, B2	[478-481]
	Cold stress -cold water stress -cold water hypothermia	A3, B1, B2, C1, C3	[482]
IV-B4	Force/ Pressure/ Physical Trauma		
	Traumatic brain injury	A4, B2, B9, C1, C3, D1	[483-486]
	Head trauma -history of head trauma -closed head injury -axonal injury	A1, B1, B8, B9, C1, C3, D1	[487-490]
	Spinal cord injury	A1, A4, C3	[491]
	Mechanical stress -Valsalva maneuver -repetitive heavy lifting -repetitive strong cough -accumulated mechanical stress	A1, A3, B1, B2, D1	[492-493]
IV-C	**OTHER**		
	Oxygen alterations -hyperoxia -hypoxia	A1, A3, A4, A7, B2, C3	[494-495]

V	**PSYCHOSOCIAL/SOCIOECONOMIC**		
V-A	**PSYCHOLOGICAL**		
	Chronic stress -repeated stress -chronic mild stress -chronic psychological stress -multiple chronic stresses -behavioral stress -childhood trauma -bereavement -chronic restraint stress -high job stress -low level of job control	A4, A6, A7, B1, B2, B9, C1, C3, D1	[496-503]
	Low mental activity -low cognitively engaging activity -low purposeful activities -low leisure activities/low hobbies --low music/drawing/meditation/reading/arts/ crafts	B5, C3, D1	[504-507]
V-B	**SOCIOLOGICAL**		
	Social isolation -isolation -loneliness -living alone -unmarried -maternal separation -low social activity index -low social support at work -constricted life space	A3, B1, B2, B8, C1, C3, D1	[508-513]
	Low education -illiteracy	D1	[514-516]
V-C	**ECONOMIC**		
	Early life socioeconomic circumstances	C3	[517]

2-7C1. Analysis of Results in Table 2-7C

The findings in the Lifestyle, Iatrogenic, Biotoxic Agents, Occupational/ Environmental Exposures, and Psychosocial/Socioeconomic categories will now be examined by sub-category. The sub-category alphanumerical headings correspond to those in Table 2-7C.

I. Lifestyle

Lifestyle includes choices mainly under individual control, and is divided arbitrarily into Diet, Activity, Substance Abuse, Other.

I-A. Diet

Poor diet reflects the adverse effects of excesses and deficiencies of dietary components. It has been used to induce myriad diseases in test animals, and it was a critical disease factor from many epidemiological and case studies.

I-A1. Dietary Excesses

Dietary excesses include: high-fat; diabetogenic diet; high-calorie; high-salt; high-carbohydrate; high advanced glycation end products (AGEs); high-cholesterol; high-iron; high-meat; high arachidonic acid; high methionine; high copper; high zinc; high pickle diet; high unfermented soy; and high-temperature cooking that results in harmful products (e.g., AGEs, nitrosamines, polycyclic aromatic hydrocarbons, and acrylamides).

As Table 2-7C shows, high-fat diet (from the specific types of fat listed in the table) had impacts at the cellular, biomarker, performance, and disease categories listed in Table 2-7B. These high-fat diets were 1) directly related to AD, 2) indirectly related to AD through their direct impact on other diseases directly related to AD (e.g., metabolic syndrome, diabetes), and 3) indirectly related to AD through their direct impact on the pre-disease surrogate endpoints directly related to AD. High-fats were also a key component of the diabetogenic diet listed in the table.

High-calorie and high-salt diets had both direct and indirect relationships to AD. High-carbohydrate diet, especially refined carbohydrates/sugars, also had full spectrum impacts. They also contributed to the diabetogenic diet.

High-AGEs, high-cholesterol, high-iron, and high-meat diets are intertwined, to a large extent. Meat tends to be high-cholesterol, high-iron, and, especially when cooked at high temperatures, associated with production of high AGEs. Most of the articles related to meat consumption and AD emphasized adverse effects. Unfortunately, in most of these meat studies, especially epidemiological studies on humans, there was no separation of confounding effects.

Most meat available to the American public comes from CAFO (confined animal feeding operations). These animals are raised confined in very close quarters. To reduce infections from such close confinement, animals are given antibiotics, and to increase growth more rapidly, animals are given synthetic growth hormones. Their feed is grain-based, not the grass they would have if pasture-raised. Would the dementia-related diseases associated with meat consumption in the articles be as copious and serious for pasture/grass-fed animals not raised under confined conditions, and not given antibiotics and synthetic growth hormones?

Most meat eaten is cooked, much of it at high temperatures, usually in the presence of endogenous and exogenous additional fats. High-temperature cooking, especially of animal foods that are high in protein and fat, results in substantial production of AGEs and other harmful substances (e.g., nitrosamines, polycyclic aromatic hydrocarbons, and acrylamides). How are the harmful effects of the cooking separated from the harmful effects of the meat? Separation was not evident in any papers

examined. The bulk of the biomedical literature has not demonstrated that meat from 'organic' pasture-raised grass-fed animals not fed antibiotics and growth hormones and not cooked at high temperatures is equally harmful to CAFO meat consumed by the vast majority of the American public, and there is some evidence that a moderate amount of high-quality meat may be beneficial.

Finally, diets high in arachidonic acid, methionine, copper, zinc, pickles, and unfermented soy contribute directly or indirectly to the development of AD.

1A2. Dietary Deficiencies

Many deficiencies listed in the literature may be symptoms of metabolic problems, not foundational causes in the present sense. Thus, a Vitamin A deficiency may be caused by 1) insufficient Vitamin A intake (foundational cause), or 2) some metabolic problem that results in reduced Vitamin A levels (symptom). Dietary deficiencies include **low**: vitamins, especially Vitamins B (B2, B6, B12, folate/folic acid, thiamine), C, D, E; minerals, especially potassium, iron, zinc, magnesium, calcium, selenium; calories (starvation, malnutrition, early life nutrient restriction); water (dehydration); glucose; glutathione; linoleic acid; docosahexaenoic acid; tryptophan; alcohol (nondrinkers); flavonoids/flavanols (cocoa, coffee, acacetin, aminogenistein, apigenin, kaempferol, 7,8-Dihydroxyflavone, anthocyanins, atriplex laciniata L, curcumin, cyanidin, datiscetin, delphinidin, EGCG, epicatechin, Epimedium brevicornum, fisetin, genistein, ginkgo, glycitein, icariin, isoscutellarein 7-O-[6'''-O-acetyl-beta-D-allopyranosyl-(12)]-beta-D-glucopyranoside, isovitexin, morin, myricetin, nobiletin, pelargonidin, phloridzin, rutin, salvigenin, Scutellaria baicalensis Georgi, Sideritis flavonoids, vitexin, xanthomicrol, luteolin, morin, PD98059, quercetin, taxifolin, β-naphthoflavone); fruit (blackberries, blueberries, strawberries, raspberries, cherries, oranges, plums, prunes, red grapes, pomegranates, date palm fruits); vegetables, especially cruciferous, dark and green leafy; fatty fish.

A very clear message about the dietary contribution to AD can be extracted from the above picture of dietary excesses and deficiencies. From the macro perspective, the amounts of fat, salt, sugar, refined carbohydrates, calories, and meat need to be reduced strongly, along with high temperature cooking, and the amounts of vitamin and mineral-laden fruits, vegetables, and fatty fish need to be increased substantially to reduce the risk of AD and perhaps contribute to reversal of AD.

I-A3. Food Additives

Many food additives are accompanied by adverse effects, and these effects may be under-diagnosed and under-researched. Many of the excesses and deficiencies mentioned above are the result of substances being added to, or removed from, the fresh whole food.

Additives include preservatives, monosodium glutamate, menadione, cysteine, diacetylcysteine, and diacetyl. Depending on how one defines "food additives", those additives with the widest impacts tend to include the major items listed under excesses above, such as fat, sugar, and salt. These components are typically added to foods for taste enhancement, not nutritional improvement. The effects of these additives appear to be at the cellular and biomarker levels.

I-B. Activity

The main sub-categories of Activity are exercise, sedentary lifestyle, and sleep.

I-B1. Sedentary Lifestyle/Lack of Exercise

The sedentary lifestyle, including low exercise, low physical activity, low daily gardening, low walking, and chronic immobilization, was mentioned quite often, and cognitive inactivity also received some mention. The resultant low cardiovascular fitness was also emphasized.

Sleep

Circadian disruption and poor sleep/sleep deprivation were also mentioned, although the main foundational components of poor sleep would be 1) choosing to sleep less or 2) not practicing good sleep-preparation habits. Other contributing factors to poor sleep, such as excessive pain, anxiety, etc, may be less under one's control, and are not regarded as foundational under the definition in the present monograph.

I-C. Substance Abuse

Substance abuse includes "recreational" drugs of all types (cocaine, methamphetamine, etc), other substances such as laxatives, common household products not usually identified as recreational drugs (such as mothballs), and especially excessive cigarette smoking and alcohol. The main substance abuse contributing factors to AD for the present study were 1) recreational drugs (especially cocaine, amphetamines/3,4-Methylenedioxyamphetamine (MDMA - Ecstacy), phencyclidine, opioids) and 2) excessive smoking and alcohol. The bulk of the studies showed the recreational drugs' contributions to AD surrogate endpoints, such as neurodegeneration markers and cognitive dysfunction.

Potential Synergies

The individual AD foundational causes identified with Lifestyle are usually studied in isolation, and synergistic effects are typically not identified. Given the number of Lifestyle component combinations that could potentially be synergistic, and adding in

1) the foundational causes from the remaining categories (identified in Table 2-7C) to the potential combinations, and

2) potential foundational causes that surface only when operating in synergy but which have not yet been identified in Table 2-7C as individual foundational causes,

it is clear that only the tip of AD foundational causes iceberg is being identified in this study.

II. Iatrogenic

Iatrogenic reflects diseases, symptoms, and injuries resulting from medical treatment, and is divided into four sub-categories: Drugs; Radiotherapy; Surgeries/ Invasive Procedures; Diagnostic Agents/Procedures. Iatrogenic is a substantial category, due mainly to the large numbers of drugs and surgeries that have side-effects and complications. The main categories, along with detailed drugs and surgeries, are presented in Table 2-7C.

II-A. Drugs

While the drug categories have some overlap, each drug is listed in one category only in Table 2-7C for purposes of brevity when generating the drug categories. The more frequently a drug is used, or the more frequently surgery or invasive treatments are employed, the more opportunity for side-effects and complications, and the more opportunity for publications describing these side-effects and complications. This study does not provide an indication of how often such side-effects and complications would occur as a percentage of use.

There were eighteen major drug categories identified in Table 2-7C, but only those with substantial entries will be discussed in this narrative. These include anti-neoplastic agents, cardiovascular agents, the massive category of central nervous system agents, hematologic agents, steroids/hormones, antihypertensive agents, and gastrointestinal agents.

What the table does not show is the effect of drug-drug combinations, or drug-other agent combinations. The effects of these combinations could be important, but might not surface in some types of studies. A study on drug-drug combinations concluded that, of approximately 11,000 drug products on the US market, trillions of clinical trials would be required to provide an evidentiary basis of safety for all combinations of ten drugs [518]. Even for all combinations of three drugs, the number of clinical trials required to evaluate safety, or lack thereof, would be astronomical.

Thus, there are many ways that 1) a drug that has been shown to contribute to AD in isolation, when combined with two other drugs that have not been shown to contribute to AD in isolation, could in aggregate have a much stronger contribution to AD, and/or 2) three drugs that have been shown to have a modest contribution to AD in isolation, when combined, could in aggregate have a much stronger contribution to AD, and/or 3) three drugs that have been shown to have negligible contribution to AD in isolation, when combined, could in aggregate have a strong contribution to AD. Even if there are small numbers for any one combination of three drugs, when they are aggregated over the total number of potential combinations, this could add up to a large number of strong contributions. This effect might not surface in any epidemiological study because 1) it would fall beneath the statistical radar screen, 2) temporal variation in the combinations would be difficult to assess, and 3) the numbers of clinical trials required to assess the impact of drug combinations are astronomical and would be impractical. For combinations of drugs larger than three, which increase for people as they age [518], the numbers of combinations and clinical trials to demonstrate safety increase rapidly.

II-A1. Antineoplastic Agents

This is a powerful class of drugs, and they tend to exert toxic/destructive effects on cancer cells. It is therefore unsurprising that these drugs would result in surrogate endpoint effects such as neurotoxicity/neurodegeneration/apoptoses on some healthy cells as well. The types of impacts in Table 2-7C bear this out. Neurotoxic-type effects are seen for many of the agents, as well as the accompanying memory degradation, but direct links to AD are not reported as frequently. The old dictum "absence of evidence is not evidence of absence" should be a warning flag on drawing hard conclusions about direct links.

II-A4. Cardiovascular Agents

The impacts of the four agents/agent classes (isoproterenol, atropine, D-ribose, muscarinic receptor antagonists) presented in Table 2-7C concentrate on the surrogate endpoints, with emphasis on the biomarkers (increase tau, Abeta) and performance (decrease memory, cognition).

II-A5. Central Nervous System Agents

This was by far the largest category of potential contributors to AD. This should not be surprising, since the members of this category act on the central nervous system (and some on the peripheral nervous system as well), and the brain is an integral part of the central nervous system. The impacts of the myriad contributing factors in this category differ somewhat by sub-category.

The analgesics and pain relievers (anesthetics/opiods) sub-category, consisting of acetaminophen, barbital, barbitone, desflurane, dexmedetomidine, diethylbarbituric acid, diethylmalonyl urea, enflurane, halothane, isoflurane, ketamine, medinal, morphine, nitrous oxide, pentobarbital, propofol, psychotropic drugs, sevoflurane, sodium diethylbarbiturate, veronal, affected all four impact areas. There was a substantial literature on the AD-related impacts of these sub-category members. One analytic problem deriving from this observation is that the relationship between the types of surgery to AD is conflated with the relationship between the anesthetic to AD, and it is difficult to separate the two, since anesthetics are used almost universally in surgery, especially major surgery.

The movement stabilizer sub-category, consisting of the anticholinergic medications doxepin, chlorpheniramine, oxybutynin, trihexyphenidyl, propiverine, L-DOPA/dopamine, was less numerous in terms of publications than the anesthetic sub-category, but covered the four impact classes as well.

The depressant/antidepressant sub-category, consisting of selective serotonin re-uptake inhibitors, benzodiazepine, dizocilpine, and 3-quinuclidinyl benzilate, had impact on performance and AD in the references shown. The absence of impact at the cellular and biomarker levels could mean that these classes of impacts were not the objectives of the research that was conducted, or they were reported in other papers not presented here.

The mood stabilizer sub-category, consisting of clozapine, methyllycaconitine, dihydro-beta-erythrodine, and anisomycin, impacted across the surrogate endpoints.

II-A7. Hematologic Agents

The main component of this category is the anti-coagulant sub-category, consisting mainly of the sulfated glycosaminoglycans heparin/heparan sulfate, dextran sulfate, pentosan polysulfate, chondroitin sulfate, dermatan sulfate, and fluindione.

II-A8. Steroids/Hormones

The substances in this category include corticosteroids (methylprednisolone, dexamethasone), anabolic androgenic steroids (nandrolone, stanozolol), corticosterone, Wortmannin, 17beta-trenbolone, salmon calcitonin, human chorionic gonadotropin, corticotrophin releasing factor, sex steroid hormones (transient testosterone treatment, flutamide), U18666A, allopregnanolone, medroxy-progesterone acetate, androgen deprivation therapy, postmenopausal hormone therapy, testosterone depletion, human chorionic gonadotropin, prenatal sex hormone exposure, and the deficiency of leptin. This class of pharmaceuticals (especially the corticosteroids) is used for a wide spectrum of medical conditions, and

the broad scope of potential impacts is concerning. While some of the drugs in the larger Iatrogenic category have rather narrow applications, the long-term effects on neurodegenerative diseases of widely used drugs such as anesthetics and steroids should be cause for serious concern.

II-A9. Antihypertensive Agents

These agents include ACE inhibitors, ICI 118,551/Selective beta2AR antagonists, telmisartan/olmesartan, and Mecamylamine. Some of the anti-hypertensive agents listed are widely used because of the prevalence of hypertension, and their long-term effects need to be examined more closely. The main impacts listed are those on the surrogate endpoints, although the ACE inhibitors are linked to AD. The referenced papers don't report impacts at the cellular level, although, again, that does not imply the absence of such impacts.

II-A10. Gastrointestinal Agents

These agents include thiorphan/phosphoramidon, and the large class of proton pump inhibitors (omeprazole, pantoprazole, lansoprazole, esomeprazole, and rabeprazole). Again, this is disturbing for the long-term, because of the almost common-place used of this family of drugs for digestive problems.

II-B. Radiotherapy

Radiotherapy that involves the head region impacts cognition and AD.

II-C. Surgery/Invasive Treatments

The following categorization is not unique. Some procedures could be assigned to multiple categories. Surgeries/invasive procedures that contribute to AD tend to involve vessel occlusion, cerebral ischemia, broader cardiac surgery, estrogen depletion, and myriad forms of dialysis.

One interesting observation is that the surgery impacts are all on AD surrogate endpoints, not on AD directly, for the references selected. This may be due to personal choice of the authors. Some authors identified a number of surrogate endpoints that were impacted, and referred to the aggregate as Alzheimer's-like. Other authors would refer to the aggregate as Alzheimer's Disease. Since inhalation anesthesia seems to be a strong contributing factor, almost any major surgery employing this type of anesthesia would have to involve some potential risk for AD, either through the surrogate endpoints, or directly.

III. Biotoxic Agents

Biotoxic Agents reflect mainly the biological substances to which we are exposed naturally, but sometimes accidentally, and sometimes by design. This category is divided into five sub-categories: Mycotoxins; Exotoxins; Bacteria/ Fungi/ Parasites; Viruses; Other. Biotoxins contributing to AD include some mycotoxins, but mainly exotoxins, bacteria, and viruses.

III-A. Mycotoxins

Only a few mycotoxins were identified, including ochratoxin A, fumonisin B1, and macrocyclic trichothecenes. Their impacts cover all four levels.

III-B. Exotoxins

Many exotoxins were identified, including excitotoxins (kainic acid/kainate, quisqualic acid, ibotenic acid, domoic acid, quinolinic acid/quinolinate), phosphatase inhibitors (okadaic acid), excitatory amino acids, malonate, annonaceaeous acetogenins, cyanobacteria (beta-N-methylamino-L-alanine/BMAA, saxitoxin, anatoxin-a, blue-green algae, microcystin), diphtheria toxin, pseudomonas aeruginosa exotoxin Y, saporins (192 IgG-saporin, p75-saporin), cycad plant (cycasin/methylazoxymethanol), glutamate/glutamine synthetase, mitochondrial inhibitors (rotenone, 3-NPA, antimycin, KCN, oligomycin). Some substances in the Other category could have been assigned to the Exotoxin category. The impacts were heavily weighted toward the cellular and biomarker levels, less so toward the performance level, and even less toward the disease level.

III-C. Bacteria/Fungi/Parasites

Myriad bacteria, fungi, and parasites (shown in Table 8-3) are dominant in sub-category III-C. The bacteria/bacterial infections include bacterial endotoxins, bacterial lipopolysaccharide, gram-negative bacterium, spirochetes, Chlamydophyla pneumoniae, Helicobacter pylori, Escherichia coli, Treponema pallidum, Tannerella forsythia, Treponema denticola, T. socranskii, T. pectinovorum, T. medium, T. amylovorum, T. maltophilum, Fusobacterium nucleatum, Prevotella intermedia, Chlamydia pneumoniae, Porphyromonas gingivalis, propionibacterium acnes, Treponemas, T. lecithinolyticum, and Borrelia burgdorferi. Bacteria are somewhat ubiquitous, so the flexibility of cause removal for items in this sub-category is much less than for items in the Lifestyle and Iatrogenic categories.

The fungi/fungal infections include Cryptococcus, Coccidioides, Aspergillus, Histoplasma, Blastomyces, C. famata, C. parapsilosis, C. glabrata, C. krusei, Candida albicans, Candida ortholopsis, Candida tropicalis, Cladosporium, Malassezia globosa, Malassezia restricta, Neosartorya hiratsukae, Phoma, Sacharomyces cerevisae, and Sclerotinia borealis.

The parasites include Trypanosoma brucei rhodesiense, Trypanosoma brucei gambiense, Acanthamoeba, Balamuthia mandrillaris, Toxoplasma gondii, Taenia solium, Toxocara canis, T. cati, Toxocara ova, and Leishmania amazonensis.

III-D. Viruses

Myriad viruses (shown in Table 2-7C) are dominant in sub-category III-D. These viruses include Bornaviridae (Mammalian 1 bornavirus), Bunyaviridae (Hantavirus, La Crosse encephalitis virus), Coronaviridae (Human coronavirus OC43, Murine hepatitis virus), Flaviviridae (Hepatitis C virus, Japanese encephalitis virus, Murray Valley encephalitis virus, St. Louis encephalitis virus, West Nile virus), Hepadnaviridae (Hepatitis B virus), Herpesviridae (Cytomegalovirus, Epstein-Barr virus, Herpes simplex virus 1, Human herpesvirus 6), Orthomyxoviridae (Influenza A virus (H1N1), Influenza A virus (H3N2), Influenza A virus (H5N1)), Paramyxoviridae (Hendra virus, Measles virus), Picornaviridae (Enterovirus 71, Theiler's murine encephalomyelitis virus), Polyomaviridae (Simian 40 virus large T antigen), Retroviridae (Human immunodeficiency virus 1, Human T-cell leukemia virus, Moloney murine leukemia virus), Rhabdoviridae (Chandipura virus), Togaviridae (Chikungunya virus, Eastern equine encephalitis virus, Venezuelan equine encephalitis virus).

Based on the volume of records examined in the bacteria/fungi/viruses categories, linkages to tau and Abeta pathologies were mentioned often, as were direct linkages to AD. Neuroinflammation induced by bacterial and viral infections appeared to be responsible for some of the tau pathology.

III-E. Other

The category named Other contains myriad substances, which are listed in Table 2-7C. It includes some plant-based contributing factors (e.g., 12-myristate 13-acetate, Forskolin, arecoline hydrobromide, quisqualate, etc), and a very substantial number of endogenous substances that were administered exogenously (e.g., 27-hydroxycholesterol, acetylcholinesterase, Bradykinin, CD40, etc).

Ordinarily, endogenous substances are not foundational causes, but intermediate causes, since their harmful effects typically are driven by other foundational causes. However, for consistency, if an endogenous substance was administered exogenously for purposes of experimentation or trial, it was considered as an exotoxin or other foundational cause for the purposes of this monograph. Thus, amyloid beta, an endogenous substance, could be viewed as an endotoxin when internal processes are being discussed, but also as an exotoxin when administered in laboratory experiments.

Because of the heterogeneity of the myriad substances in this class, specific impact statements need to be tailored to the specific members of this class. However, from an overall perspective, the majority of impacts are at the cellular and biomarker levels, much fewer impacts at the performance level, and very few impacts at the disease level. It should be cautioned again that the absence of impacts reported should not be interpreted as their non-existence. They may not exist, they may exist and were not an objective of the research, or they may exist and were not reported.

IV. Occupational/Environmental Exposures

IV-A. Chemicals/Materials

IV-A1. Industrial and Household Chemicals/Materials

This sub-category is very broad. There is overlap among the next level taxonomy elements; for example, some of the solvents are hydrocarbons and some of the chemical compounds are hydrocarbons.

This sub-category includes hydrocarbons, solvents, chemical compounds, and Other.

The hydrocarbons sub-category includes, e.g., methylcholanthrene, polycyclic aromatic hydrocarbons, diesel fuel, kerosene, etc.

The solvents sub-category includes, e.g., petroleum-based solvents (mineral turpentine, diesel fuel, fuel oil, kerosene, etc), chlorinated solvents (trichloroethylene, perchlorethylene, trichloroethane, dichloromethane, benzene), organic solvents (benzene, toluene, phenols, alcohols, ketones, methylmethacrylate), dimethyl sulfoxide/ DMSO, etc. The impacts from the members of this sub-category, as reported in the references selected, tended to focus on performance and disease. This was due to a number of epidemiology studies of occupational impacts, which tend to focus on higher level impacts.

The chemical compounds/Other sub-categories include a full spectrum of chemical compounds, especially chlorine, bromine, nitrogen, sodium, sulfur, and carbon compounds. Members of these sub-categories include, e.g., Neurotoxins (6-hydroxydopamine/6-OHDA, 5,6-dihydroxytryptamine/ 5,6-DHT, -5,7-dihydroxytryptamine/5,7-DHT, Type-2 Alkenes/Reactive aldehydes (Acrolein, 4-Hydroxynonenal/HNE, Acrylamide, Methyl glyoxal), Nitrosamine/ N-nitrosodiethylamine, Adenosine, 3', 5'-cyclic monophosphate/cAMP, Carbon tetrachloride, Chemical warfare agents/ nerve agents (organophosphates, soman, sarin, ethyl S-2-di-isopropylaminoethyl-phosphonothiolate, VX, tabun), Cyanide (Potassium cyanide, Sodium cyanide), Formaldehyde, Hydrogen Peroxide/H2O2, Lipophilic chemicals (persistent organic pollutants, bisphenol A, phthalates, low molecular weight hydrocarbons, polynuclear aromatic hydrocarbons, endocrine disruptors), Sulfur dioxide/SO2, Phthalates (Di-(2-ethylhexyl)-phthalate/DEHP, mono-2-ethylhexyl phthalate/MEHP, DEHP metabolites), Brominated flame retardants (hexabromocyclo-dodecane/HBCD, tetrabromobisphenol-Al/TBBPA, decabromodiphenyl ether/DBDE, polybrominated diphenyl ethers/PBDEs), Ammonia, Hypochlorous acid/HOCl, Methanol, Peroxynitrite, Sodium azide, Acetaldehyde, 3-Bromopyruvate, Vehicular emission oxides (nitrogen dioxide/NO2, carbon monoxide/CO), Sodium fluoride, Membrane-mimicking detergents (sodium dodecyl sulfate, lithium dodecyl sulfate), Nitric oxide donors (sodium nitroprusside, DETA NONOate), Amorphous aluminosilicates, Sodium nitrite, Tert-butyl hydroperoxide/t-BHP, Alloxan, Ammonium chloride, Anionic dyes (Congo Red, Thiazine Red, Thioflavin S), Aroclor 1254, Cobalt chloride, Magnesium chloride, 2,2'-azobis(2-methylpropionamidine) dihydrochloride/AAPH, Methylglyoxal/ Glyoxal, Disuccinimidyl suberate, Naphthazarin/5,8-dihydroxy-1,4-naphthoquinone/ 5,8-dihydroxy-1,4-naphthalenedione, Pyrithiamine, Pyrogallol, Glyceraldehyde-3-phosphate/GAPDH, Ethylcholine mustard aziridinium ion/AF64A, 1-methyl-4-phenylpyridinium ion, 2,2'-dithiodipyridine, Aftin-4, Kaolin, Ozone, 2;3;7;8-tetrachlorodibenzo-p-dioxin.

The largest sub-category, by far, is the chemical compounds. This sub-category is associated with roughly even impacts at the cellular, biomarker, and performance levels. There is much less reported direct association at the disease level, for the selected references.

IV-A2. Agricultural Chemicals

This sub-category emphasizes pesticides, herbicides, insecticides, and fungicides, and includes, e.g., Organochlorine pesticides, Organophosphate pesticides, 2,4,5-trichlorophenoxyacetic acid, 2,4-dichlorophenoxyacetic acid, Agent Orange, Aldrin, Alkylphenolpolyethoxylates, APEOs, Arsenic, Beta-hexachlorocyclohexane/beta-HCH, Bipyridyles, Carbamates, Carbofuran, Chlorfenvinphos, Chlorpyrifos/ CPF, Cycloheximide, Cypermethrin, Deltamethrin, Dichlorodiphenyldichloroethylene/DDE, Dichlorodiphenyltrichloroethane/DDT, Dichlorodiphenyldichloroethane/DDD, Dieldrin, Dimethyl parathion, Endosulfan, Famoxadone, Fenamidone, Glyphosate, Hexachlorobenzene, Hexachlorocyclohexane/HCH, Imidacloprid, Lindane, Maneb, Methamidophos, Methyl parathion, Neonicotinoids, Nonylphenol, Octylphenol, Paraquat, Parathion, Pyraclostrobin, Pyrethroids, Trans-nonachlor, Trichlorfon/TCF, Trifloxystrobin, etc.

Adverse impacts span the cellular, biomarker, performance, and disease levels. These chemicals impact the larger population through the food supply, and have devastating effects on the agricultural workforce. Given the ubiquitous nature of agricultural chemicals and industrial/household chemicals in daily life, eliminating them will be challenging.

IV-A3. Materials

The materials/particulates that constitute this category are broadly-based, and in many cases have become part of the average lifestyle. Some examples include:

-heavy metals (e.g., aluminum, arsenic, cadmium, calcium/Ca2/CaCl, calcium ionophore/A-23187/calcimycin , cobalt, copper, iron, lead, manganese, mercury , methylmercury, selenium, tin, zinc, etc)

-particulates (e.g., air pollution, surgical smoke, dust, etc)

-nanoparticles (e.g., iron nanoparticles, titanium dioxide nanoparticles, CdSe quantum dots, diesel exhaust nanoparticles, alumina nanoparticles, manganese oxide nanoparticles, copper nanoparticles, silicon dioxide nanoparticles, zinc oxide nanoparticles, silver nanoparticles, nickel nanoparticles, etc)

Impacts of these materials through diverse ingestion pathways cover the full spectrum of levels. Both metals and small sized particles have adverse effects. When the two are combined, the synergy becomes problematical. Metallic particles within the nanoparticle range (<100 nm) are able to cross many internal protective barriers, including the blood-brain-barrier (BBB), and cause myriad problems. While penetration of the BBB by nanoparticles is sometimes used for drug delivery, unwanted penetration (as reflected in the present study's references) can be quite harmful.

IV-B. Physical/Mechanical

This sub-category includes ionizing radiation, non-ionizing non-visible radiation, non-ionizing visible radiation, sound radiation, temperature fields, and force fields.

The ionizing radiation component includes, e.g., gamma radiation (dental X-rays, gamma rays, etc), particle radiation (56Fe-particle radiation, cosmic radiation, HZE particle radiation), radionuclide pollutants (uranium, cesium, cobalt, radon). The main impacts focus on the biomarker and performance levels, with some at the cellular levels and much less at the disease level.

The non-ionizing non-visible radiation component includes, e.g., electromagnetic fields at myriad frequencies, such as extremely low frequency/ELF-EMF, 900 MHz radiofrequency (RF), electromagnetic pulse/EMP, electroconvulsive shock/ECS, UV irradiation, etc. The references selected emphasize biomarker level impact, then performance level impacts, and some links to AD.

The non-ionizing visible radiation component includes e.g., UV irradiation, photolysis of 1-(2-nitrophenyl)ethyl sulfate, with impacts emphasizing Abeta production.

The sound radiation component includes, e.g., short-lasting impulse noise, chronic noise exposure, night-time aircraft noise, ultrasound sonication, etc. While impacts are identified at the cellular, biomarker, and disease levels, Abeta generation and exacerbation are emphasized.

The thermal component includes, e.g., cold water hypothermia, cold water stress, heat shock, heat stress, heating, hyperthermia, etc, and impacts the cellular, biomarker, and performance levels.

The physical force component includes, e.g., blasts, blast traumatic brain injury, hippocampal injury, accumulated mechanical stress, spinal cord injury, frequent strong Valsalva maneuvers, long hours of repetitive heavy lifting, sequences of blows during the playing of a wind instrument, forceful and

repetitive cough, bearing-down efforts during parturition, history of head trauma, etc. The impacts cover all four levels, with perhaps added emphasis on AD.

The main components of this sub-category, the different types of physical fields with which we interact (electromagnetic, sound, temperature, pressure, force) are ubiquitous. Avoiding exposure to these emissions/interactions would require a major change in lifestyle (and probably location) for most people. The 'Other' category is small, and contains adverse effects from over- and under-exposure to oxygen.

V. Psychosocial/Socioeconomic

Psychosocial/Socioeconomic are those foundational causes that reflect personal problems, social interactions, larger societal interactions, and economic relationships. Psychological and sociological stress were major causative factors; economic types of stress seemed to play less of a direct role.

V-A. Psychological

This sub-category includes, e.g., chronic stress (repeated stress, chronic mild stress, chronic psychological stress, multiple chronic stresses, behavioral stress, childhood trauma, bereavement, chronic restraint stress, high job stress), low mental activity (low cognitively engaging activity, low purposeful activities, low leisure activities/low hobbies, low music/drawing/meditation/reading/arts/crafts), etc. Impacts seemed to spread out over all four levels.

V-B. Sociological

This sub-category includes, e.g., social isolation (isolation, loneliness, living alone, unmarried, maternal separation, low social activity index, low social support at work, constricted life space), low education (illiteracy), etc. Impacts cover all four levels, with emphasis on the biomarker, performance, and disease levels.

V-C. Economic

This sub-category includes, e.g., economic stress (childhood socioeconomic circumstance), etc. In this small sub-category, impact focused on cognitive deficits.

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APPENDIX 6 – TAXONOMY OF IMPACTS FROM AD FOUNDATIONAL CONTRIBUTING FACTORS

Table 2-7B - Taxonomy of Effects/Impacts from AD Foundational Causes

(adapted from reference [1])

CODE	LEVEL
	CELLULAR LEVEL
A1	increase neuroinflammation
A2	increase neurotoxicity
A3	increase neuronal death
A4	increase neurodegeneration
A5	induce DNA damage
A6	damage mitochondria
A7	increase neuronal oxidative stress
	BIOMARKER LEVEL
B1	increase tau pathology/neurofibrillary tangles
B2	increase Abeta generation
B3	increase AGEs
B4	increase insulin resistance
B5	reduce brain volume
B6	produce low tostesterone
B7	produce tissue lesions
B8	induce synaptic/neurotransmission dysfunction
B9	induce hippocampal damage
B10	induce olfactory dysfunction
B11	impair glutamate uptake
B12	compromise BBB integrity
B13	impair glucose homeostasis
B14	impair metal homeostasis
	PERFORMANCE LEVEL
C1	increase memory loss
C2	increase seizures
C3	induce cognitive dysfunction
	DISEASE LEVEL
D1	increase AD risk
D2	increase diabetes risk
D3	induce hypothyroidism
D4	induce metabolic syndrome
D5	increase obesity

These effects/impacts are divided into four categories:

- Cellular Level,
- Biomarker Level,

- Performance Level,
- Disease Level.

Each lowest-level sub-category was obtained by inspecting visually many abstracts and titles of records that related cause to effect/impact, and extracting those effects mentioned multiple times.

The lowest-level sub-categories are not orthogonal; there is some partial overlap and redundancy. Much of this is due to the different less-than-precise language of the article authors themselves. For example, some authors may use neurotoxicity to refer to neural damage, others may use neuro-degeneration or neuronal death or .....

The value of incorporating the members of the above table in the final results is that it conveys (to the research community, the medical clinician community, and the consumer community) how the research is linked either

1) directly to AD, or indirectly to AD through

2) strong disease precursors of AD (e.g., diabetes), or

3) strong behavioral precursors of AD (e.g., cognitive decline), or

4) strong biomarker precursors of AD (e.g., increase tau hyperphosphorylation), or

5) strong cellular precursors of AD (e.g., increase neuronal death).

Why is this important?

Consider two potential foundational causes of AD identified in the present study, high-fat diets and wireless radiation. High-fat-diets have been studied for a long time, and there appears to be good evidence that such diets are strong contributors to AD. The long-term data are sufficient to conclude there is a direct link between high-fat diets and AD.

Wireless radiation at cell phone radiofrequencies or WiFi frequencies has been in commercial/military use for perhaps thirty years, and in wide-scale use for perhaps ten+ years. It might take 50-60 years to identify impacts of this segment of the radiation spectrum on the development of AD. We have a choice. We can wait many decades for the types of conclusive evidence that would satisfy the statisticians, or we can start to take precautions based on the impact of wireless radiation on surrogate endpoints/biomarkers/AD characteristics already demonstrated. This is the Precautionary Principle, and the results contained in Table 2-7C provide a starting point for implementation of the Precautionary Principle for prevention and reversal of AD.

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APPENDIX 7 – AD TREATMENTS

Table 2-6

Existing AD Treatments

(arranged in decreasing order of number of records in database)

# RECORDS	TREATMENT
3174	cholinesterase inhibitor
1481	donepezil
1392	antioxidant
1219	immunotherapy
1154	antiinflammatory agents
958	memantine
903	antipsychotic agents
874	Rivastigmine
734	galantamine
661	anti-Abeta therapy
642	antidepressant
600	exercise
526	Tacrine
428	secretase inhibitors
421	psychotropic agents
408	NSAID
402	statin therapy
381	neuroleptic
333	herb
322	chelator
312	plant extract
295	nerve growth factor
294	stem cell
285	vitamin E
284	risperidone
235	antihypertensive agents
232	Curcumin
212	nicotine
210	hormone replacement therapy
210	polyphenol
209	brain-derived neurotrophic factor
195	melatonin
192	cognitive therapy
189	vitamin supplementation
188	DHA
183	olanzapine
183	walking

179	transplanted
170	flavonoids
168	anti-oxidant
163	folate
159	17 beta-estradiol
157	NMDA receptor antagonist
152	physostigmine
148	lithium
147	estrogen replacement therapy
146	vitamin B-12
144	serotonin reuptake inhibitor
143	neurotrophin
142	BACE1 inhibitor
142	quetiapine
134	omega-3 fatty acid
133	Haloperidol
131	gene therapy
130	huperzine
128	fish
123	fruit
123	psychotherapy
122	aggregation inhibitor
121	music therapy
118	ACE inhibitor
110	occupational therapy
105	acupuncture
104	social interaction
102	phenol
100	resveratrol
97	polyunsaturated fatty acids
96	neural stem cells
96	transcranial magnetic stimulation
92	vitamin D
91	selegiline
90	anticonvulsant
86	piracetam
85	citalopram
85	Testosterone
83	folic acid
83	vitamin C
82	electroconvulsive therapy
81	MAO-B inhibitor
80	muscarinic agonist
77	Epigallocatechin-3-gallate

76	clioquinol
72	ibuprofen
71	Nimodipine
70	simvastatin
69	Carbamazepine
68	rapamycin
67	clozapine
66	caffeine
66	calcium channel blocker
66	cannabinoid
64	EGB 761
62	tetrahydroaminoacridine
61	alpha tocopherol
61	antiepileptic drugs
61	leisure activity
60	Ginseng
60	Mediterranean diet
60	Phytochemical
59	acetyl-L-carnitine
59	metrifonate
58	Aricept
58	Bapineuzumab
57	mesenchymal stem cells
56	trazodone
55	Retinoic acid
54	Cerebrolysin
54	GSK-3 inhibitor
53	humanin
53	reminiscence therapy
52	B vitamin
52	sertraline
52	solanezumab
51	Ginsenoside
50	aerobic exercise
50	pioglitazone
49	deep brain stimulation
49	indomethacin
49	leptin
48	aromatherapy
48	deprenyl
48	insulin therapy
48	Intravenous immunoglobulin
47	antidiabetic agents
47	galanin

47	selenium
47	treadmill
46	coffee
46	DHEA
46	diuretic
46	progesterone
45	Atorvastatin
45	massage
44	electroacupuncture
44	fluoxetine
44	memory training
44	phosphatidylserine
44	rosiglitazone
43	phosphatidylcholine
43	semagacestat
42	cholesterol-lowering agents
41	COX-2 inhibitor
41	Physiotherapy
40	Aripiprazole
38	bright light therapy
38	quercetin
37	fish oil
36	phenserine
36	S-adenosylmethionine
36	saponin
35	spice
34	alpha lipoic acid
34	amylin
34	environmental enrichment
34	PPARgamma agonist
34	Propentofylline
34	social activity
34	vitamin B6
33	cobalamin
33	flurbiprofen
33	methylene blue
33	sensory stimulation
32	anti-tau treatments
32	metformin
32	rasagiline
31	Group Therapy
30	catechin
30	coumarin
30	lipoic acid

30	lovastatin
29	berberine
29	ferulic acid
29	latrepirdine
29	small interfering RNA
27	velnacrine
26	bexarotene
26	carotenoid
26	Citicoline
26	desferrioxamine
26	Liraglutide
26	neurosteroid
26	Thiamine
25	morphine
25	N-acetylcysteine
25	transcutaneous electrical nerve stimulation
24	amantadine
24	anti-diabetic
24	ascorbic acid
24	caloric restriction
24	erythropoietin
24	genistein
24	grape
24	lamotrigine
24	red wine
23	behavioral therapy
23	histone deacetylase inhibitor
23	medroxyprogesterone
23	methylphenidate
23	pravastatin
23	scyllo-inositol
23	Xanomeline
22	divalproex
22	gabapentin
22	isoflavone
22	lavender
22	levetiracetam
22	lipid lowering
22	raloxifene
22	RXR agonist
22	transcranial direct current stimulation
22	validation therapy
22	ziprasidone
21	arecoline

21	idebenone
21	minocycline
21	nicergoline
21	PBT2
21	perindopril
21	polysaccharide
21	soy
20	angiotensin receptor blockers
20	anti-depressant
20	Chondroitin sulfate
20	etanercept
20	genetic deletion
20	hydergine
20	piperidine
20	sodium valproate
20	sulfonamide
19	animal-assisted therapy
19	clonazepam
19	Colostrinin
19	deferoxamine
19	multisensory stimulation
18	allopregnanolone
18	buspirone
18	butyrylcholinesterase inhibitor
18	clonidine
18	coenzyme Q10
18	cyclophilin
18	fluvoxamine
18	garlic
18	Imipramine
18	tarenflurbil
17	AF102B
17	anthocyanin
17	citrus
17	embryonic stem cell
17	escitalopram
17	Higher education level
17	hydrogen sulfide
16	Alpha2 macroglobulin
16	Amaryllidaceae
16	aminoguanidine
16	art therapy
16	benzothiazole
16	Caffeic acid

16	Crocus sativus
16	doxycycline
16	Eptastigmine
16	exendin-4
16	gelsolin
16	Icariin
16	M30
16	resistance training
16	Tai Chi
16	tanshinone
16	Vinpocetine
16	Yizhi
15	anti-amnesic
15	Bacopa
15	cocoa
15	gantenerumab
15	Geniposide
15	moxibustion
15	oxiracetam
15	Reality orientation therapy
15	rifampicin
15	strength training
14	9-Amino-1,2,3,4-tetrahydroacridine
14	apigenin
14	cinnamon
14	D-cycloserine
14	propargylamine
14	rosmarinic acid
14	telmisartan
14	topiramate
14	Tramiprosate
13	blueberry
13	Fortasyn
13	hyperforin
13	Kampo
13	ladostigil
13	mirtazapine
13	N-benzylpiperidine
13	Panax notoginseng
13	Salvia miltiorrhiza
13	Taurine
13	TV3326
13	yoga
12	aniracetam

12	anti-epileptic
12	CHF5074
12	dantrolene
12	Ghrelin
12	hyperbaric oxygen
12	linopirdine
12	multinutrient
12	oleic acid
12	propranolol
12	pyridostigmine
12	trehalose
11	AF150
11	anticoagulant therapy
11	captopril
11	lycopene
11	nootropic agents
11	piperazine
11	Polygala tenuifolia
11	ramelteon
11	Riluzole
11	tiapride
10	antibiotic therapy
10	beer
10	clomipramine
10	dance therapy
10	Doll therapy
10	fatty acid supplementation
10	gold nanoparticles
10	Huannao Yicong
10	lentiviral vectors
10	Luteolin
10	memoquin
10	Nefiracetam
10	pitavastatin
10	pomegranate
10	Puerarin
10	rhynchophylline
10	zolpidem
9	acupressure
9	AF267B
9	anandamide
9	apomorphine
9	ASS234
9	butylphthalide

9	dihydrotestosterone
9	glatiramer acetate
9	horticultural therapy
9	ketogenic diet
9	losartan
9	rutin
9	Zingiber
8	7,8-dihydroxyflavone
8	Aducanumab
8	amiridin
8	apocynin
8	baicalein
8	Centella asiatica
8	Danshen
8	edaravone
8	focused ultrasound
8	HP 029
8	Huprine
8	milieu therapy
8	paeoniflorin
8	R-flurbiprofen
8	Sodium selenate
8	Withania somnifera
7	Acori graminei
7	akatinol
7	beta-asarone
7	cotinine
7	cryptotanshinone
7	cyproterone
7	dronabinol
7	ganstigmine
7	genetic reduction
7	laser therapy
7	Lavandula angustifolia
7	naringenin
7	Noopept
7	oleocanthal
7	pepper
7	pet therapy
7	ponezumab
7	Pyritinol
7	Rehmannia glutinosa
7	Salidroside
7	Salvianolic acid

7	silymarin
7	T0901317
7	Tauroursodeoxycholic acid
7	thalidomide
7	triflusal
7	Triptolide
7	valsartan
6	Colivelin
6	fullerene
6	gastrodin
6	hesperidin
6	JWH-133
6	Naftidrofuryl
6	naringin
6	neuroglobin
6	nobiletin
6	Oleuropein aglycone
6	sodium butyrate
6	talsaclidine
6	Tannic acid
6	Tetrahydrohyperforin
6	Tiaoxin
6	xanthoceraside
5	4-Phenylbutyrate
5	asiatic acid
5	benzylpiperidine
5	Capsaicin
5	Carnosic acid
5	Catalpol
5	D609
5	Danggui-Shaoyao-San
5	dihydroergotoxine
5	ellagic acid
5	fingolimod
5	FLZ
5	glycosaminoglycan polysulfate
5	granulocyte colony-stimulating factor
5	graphene
5	IKKbeta
5	mifepristone
5	osthole
5	protocatechuic acid
5	Qingxin Kaiqiao
5	S14G-HN

5	Selenomethionine
5	umbilical cord blood cells
5	vagus nerve stimulation
5	Wuzi Yanzong
5	Xiusanzhen
5	yi-gan
4	Abeta12-28P
4	carvedilol
4	Choto-san
4	cyclandelate
4	cytidinediphosphocholine
4	ebselen
4	fucoidan
4	H-89
4	Hericium erinaceus
4	JTP-4819
4	L-theanine
4	low molecular weight heparin
4	Namaste Care
4	Naoling
4	neotrofin
4	Noninvasive Brain Stimulation
4	NRG1
4	Oligonol
4	red mold
4	S-allyl-l-cysteine
4	Scutellaria baicalensis
4	spatial training
4	SuHeXiang
4	Tolfenamic acid
4	Tong Luo Jiu Nao
4	touch intervention
4	Valeriana amurensis
3	15d-PGJ2
3	17-AAG
3	4-O-methylhonokiol
3	alpha-Mangostin
3	Anatabine
3	angiotensin-(1-7)
3	Arundic acid
3	bee venom
3	betaine
3	Cinnamomum
3	coconut

3	coptisine
3	corticotropin-releasing factor receptor
3	Cranberry
3	diallyl disulfide
3	Emblica officinalis
3	Fucoxanthin
3	Fuzhisan
3	Gamma-hydroxybutyrate
3	intermittent fasting
3	Isradipine
3	morin
3	neuritin
3	pifithrin-alpha
3	PQCA
3	s-Ethyl cysteine
3	s-propyl cysteine
3	sulforaphane
3	tamibarotene
3	targretin
3	tenuifolin
3	Tetrandrine
3	Thymoquinone
3	tropisetron
3	vildagliptin
2	3,6'-dithiothalidomide
2	4% figs
2	6-shogaol
2	A-887755
2	Activated protein C
2	AF151
2	Agmatine
2	aminopyridazines
2	apple juice concentrate
2	arachidonic acid ARA
2	AVP-786
2	benfotiamine
2	BMS-299897
2	bone morphogenetic protein 9
2	compound-1
2	CREB-binding protein CBP
2	crocetin
2	Cystatin B deletion
2	dasatinib
2	delta-9-tetrahydrocannabinol

2	derivative of benzothiazole aniline
2	diazoxide
2	Dl-PHPB
2	Drp1 inhibitors
2	Enoxaparin
2	ergothioneine
2	Fbx2
2	glutaminyl cyclase inhibitor
2	glycyrrhizic acid
2	Gossypium herbaceam
2	Human amniotic epithelial cells
2	hunger
2	Hydroxysafflor yellow
2	ICI 118,551
2	IL-33
2	ILEI
2	indirubin-3'-monoxime
2	iododiflunisal
2	isoliquiritigenin
2	L803-mts
2	linagliptin
2	Memogain
2	Meserine
2	mithramycin
2	MMP9 gene
2	Ophiopogon japonicus
2	PEI-conjugated R8-Abeta(25-35)
2	phloroglucinol
2	PLD2 ablation
2	prolyl endopeptidase inhibitor
2	protein-iPSCs
2	RNS60
2	Safflower yellow
2	salubrinal
2	saxagliptin
2	Sendai virus
2	single-walled carbon nanotubes
2	Smart Soup
2	sodium benzoate
2	T-817MA
2	tetrathiomolybdate
2	WAY-100635
2	WIN55212-2

1	2-methyl-5-(3-{4-[(S)-methylsulfinyl]phenyl}-1-benzofuran-5-yl
1	2-phenylethynyl-butyltellurium
1	2S -neoeriocitrin
1	3,4-dihydroxyphenylethanol
1	3-alpha-akebonoic acid
1	40 Hz light-flickering regime
1	AA3E2
1	AAD-2004
1	AAV-p75ECD
1	Abeta-HBc VLPs
1	ACAT1 gene ablation
1	Activase rt-PA
1	activation-inhibitory Lactobacillus pentosus
1	AD-35
1	adipose-derived stem cell-conditioned medium
1	allicin
1	alpha-chymotrypcin
1	alpha-Zearalanol
1	Anhydroexfoliamycin
1	anthoxanthin
1	anti-dementia effects of s-limonene
1	arctigenin
1	AS2030680
1	AS2674723
1	ASP5736
1	AVP-923
1	beta-caryophyllene
1	Bis(9)-(-)-nor-meptazinol
1	BMS-289948
1	BMS-708,163
1	BRET-Qdot-emitted NIR
1	butyrolactone
1	C-30-27
1	Cardiotrophin-1
1	Cassia obtusifolia
1	Centipedegrass
1	chitosan oligosaccharides
1	chloroquine derivatives
1	ciproxifan
1	collagen VI
1	Cudrania cochinchinensis
1	Cyperus rotundus

1	cytosine-guanosine-containing DNA oligodeoxynucleotides
1	DA-JC4
1	Dalesconol B
1	Daucosterol palmitate
1	DcR3
1	Dehydroevodiamine
1	deleting Nogo
1	Dendrobium Nobile Lindl
1	deoxyschisandrin
1	dexamethasone exposure during pregnancy
1	Dietary niacin
1	Dihydromyricetin
1	dipotassium N-stearoyltyrosinate
1	dynorphin A-(1-13)
1	dZip1 inhibition
1	ephrinB1/Fc
1	Eugenia jambolana
1	EUK1001
1	exogenous Abeta fibrillar seeds
1	fenugreek seed powder
1	Fructus mume
1	Fumanjian
1	Gami-Chunghyuldan
1	genetic deletion of 12/15LO
1	Genetic deletion of eIF2alpha
1	Gfa2-VIVIT
1	GSM-2
1	Harpagoside
1	hemizygous deletion of Synj1
1	high potassium intakes
1	human ApoE4 allele
1	HX630
1	hypericin
1	IL-1R blocking Ab
1	illite
1	Inhibition of GIVA-PLA(2)
1	Interleukin-34
1	iso-alpha-acids
1	JC-124
1	JM6
1	Jujuboside
1	K6Abeta1-30[E18E19]
1	kallikrein 7

1	Kamikihi-to
1	kappacarrageenanderived pentasaccharide
1	L-NNNBP
1	laminin 1
1	Lentiviral ABN
1	low-intensity pulsed LIP ultrasound
1	LX2343
1	Magnesium sulfate treatment
1	maltolyl p-coumarate
1	Marapuama
1	MER5101
1	MOG45D
1	MS-275
1	murine pathogen-free
1	MW01-2-069A-SRM
1	MW01-2-151SRM
1	N-butylidenephthalide
1	NButGT
1	Neuropep-1
1	ninjin'yoeito
1	P. frutescens extract
1	P11-hEGF
1	Paeng-Jo-Yeon-Nyeon-Baek-Ja-In-Hwan
1	Pantethine
1	pBri-peptide-based immunomodulation
1	PD146176
1	pentamidine
1	peoniflorin
1	pharmacological inducer of HO-1
1	PHF13
1	Pleurotus ostreatus
1	PP-3copy-Abeta1-6-loop123
1	pratensein
1	proteolytic nanobodies
1	Pterocarpus marsupium
1	pulsed ultrasound
1	Qifu-Yin
1	recombinant brain-targeted neprilysin ASN12
1	reduced InsP3R1 expression
1	Reduction of exosome secretion
1	repeated cognitive enrichment
1	Rhizophora mucronata
1	RP-1
1	S1 peptide

1	Saengshik
1	Salvia sahendica
1	Satureja bachtiarica
1	scanning ultrasound
1	Schisantherin B
1	selenofuranoside
1	Shengmai
1	shRNA in the dentate
1	Sia hydroxamate
1	skeletal analogues of gambierol
1	ST09
1	sulfo-muco-polysaccharides
1	sulfomucopolysaccharide
1	SUN11602
1	TAK-070
1	tangeretin
1	TAT-BDNF peptide
1	TAT-haFGF
1	tat-VIVIT
1	tenascin-C-deficient
1	TG101209
1	Tongmai Yizhi Decoction
1	tri-lithium pyrroloquinoline quinone
1	tricyclodecan-9-xanthogenate
1	unmethylated DNA CpG motif
1	Wen-Dan-Tang
1	Y-29794
1	yonkenafil
1	Zataria multiflora Boiss

(return to TOC)

APPENDIX 8 – AD TREATMENT IMPACTS

Table 2-4

DETAILED TAXONOMY OF AD TREATMENT BENEFITS

BENEFITS FROM AD TREATMENT
IMPROVE MAINLINE BIOMARKER DEFICITS
1. Neurotransmission modulation
1.101 incr cholinergic
1.102 restor SLAI
1.15 Improve synapse plasticity
1.1501 improv PLASTICITY
1.1502 reduc SREBP2
1.1503 regen neural network
1.1504 incr PSD95
1.1505 incr Ras activity
1.1506 incr CMRglc
1.1507 incr MAP1B
1.1508 reduc TOMOSYN
1.1509 reduc myoinositol
1.151 reduc S6K1
1.1511 rescu PI(4,5)P(2)
1.1512 restor SNAP-25
1.1513 decr PAK
1.1514 amelior excessive NO
1.1515 incr magnesium
1.1516 incr EAAT2
1.1517 reduc glut excitotoxicity
1.1518 decr calcineurin
1.2 Antagonize NMDA receptors
1.201 antag NMDA
1.3 GABAergic modulation
1.301 incr GABA
1.302 restor gephyrin
1.4 Serotonin receptor modulation
1.401 incr SEROTONIN
1.402 inhibit MAO
1.5 Histamine receptor modulation
1.501 incr histamine
1.502 incr T-MEHA
1.6 Adenosine receptor modulation
1.601 incr ATP
1.7 Other neurotransmitter modulation
1.701 incr norepinephrine
1.702 activat M1

1.703 incr N-acetylaspartate
1.704 incr NAAG
1.705 incr brain activation
2. Tau modulation
2.1 Tau phosphorylation inhibition
2.101 reduc hyperphosphorylation
2.2 Microtubule stabilization
2.201 restor tubulin
2.202 decr NFT
2.203 incr glutathione
2.3 Reducing Tau oligomerization/pathology
2.301 reduc tau pathology
2.302 decr paired helical filament
2.303 inhibit Hsp90alpha
2.304 prevent hsv
2.305 incr anti-tau antibod
3. Abeta modulation
3.1 Reduce Abeta
3.101 reduc Abeta
3.102 reduc mTOR
3.103 incr AMPK
3.104 incr Brn-4
3.105 incr p75ECD
3.106 incr LR11
3.107 inhibit CatB
3.108 reduc PRAS40 phosphorylation
3.109 restor glymphatic drainage
3.2 Amyloid transport
3.201 restor BBB
3.202 incr Claudin-5
3.3 Preventing amyloid aggregation
3.302 incr iPLA2
3.303 inhibit ADDL
3.304 reduc C3 convertase
3.305 incr TTR
3.306 incr LRP1
3.307 incr NEP
3.308 incr ECE-2
3.309 incr tyrosine hydroxylase
3.4 Promoting amyloid clearance
3.401 enhanc phagocytosis
3.402 restor lysosomal acidification
3.403 incr ABCA1
3.404 incr ABCA7

3.405 inhibit CD33
3.406 incr LXR
3.407 enhanc megalin
3.408 incr gelsolin
3.409 restor Pgp
3.5 Amyloid based immunotherapy
3.501 enhanc antibod
3.6 Secretase enzymes modulation
3.601 incr alpha-secretase
3.602 incr sAPP
3.603 incr nonamyloidogenic
3.604 reduc GSAP
3.605 reduc PS1
3.606 incr ADAM10
3.607 incr ADAM9
3.608 reduc BACE1
3.609 incr SIRT1
3.61 decr PICALM
3.7 Improve structural deficits
3.701 decr brain atrophy
3.8 Other
3.801 decr homocysteine
3.802 incr methionone
IMPROVE METABOLISM BIOMARKERS
4. Insulin and Energy metabolism
4.1 Insulin metabolism
4.101 allev diabet
4.102 reduc IRS-1
4.103 improv hyperglycemia
4.104 incr IDE
4.105 incr GLP-1
4.106 incr Akt
4.107 incr BAG3
4.108 incr GLUT4
4.2 Neuronal metabolism
4.201 improv metabol
4.202 incr O-GlcNAc
5. Oxidative stress reduction
5.1 Augmenting endogenous defense
5.101 improv antioxidant defense
5.102 reduc oxidative stress
5.103 incr glutathione peroxidase
5.104 decr nitrotyrosine
5.105 incr plasma Vitamin E

5.106 reduc Pr-SSG
5.107 decr ROS
5.108 incr Nrf2
5.109 incr IGF-1
5.11 reduc ADMA
5.111 decr GSK-3
5.112 improv endotheli
5.113 restor BH4
5.114 incr cerebral blood flow
5.2 AGEs reduction
5.201 reduc AGEs
6. Mitochondrial function improvement
6.101 protect mitochondria
6.102 incr SIR1
6.103 incr PGC-1alpha
6.104 decr Drp1
7. Modulation of cellular calcium homeostasis
7.101 decr calcium
7.102 reduc SOCE
8. Inflammation alleviation
8.101 reduc inflamm
8.102 decr TNF-alpha
8.103 decr CRP
8.104 incr cAMP
8.105 decr IL-1
8.106 decr IL-6
8.107 incr IL-4
8.108 reduc NF-kappaB
8.109 decr p16
8.11 incr cyclinD1
8.111 incr PPAR-gamma
8.112 inhib cyclooxygenase-1
8.113 incr resolvin D1
8.114 reduc CXCR2
8.115 reduc TLR-4
8.116 reduc MKL1
8.117 reduc s100B
9. Others
9.1 Hormone dyshomeostasis
9.101 incr progesterone
9.102 incr testosterone
9.103 replace estrogen
9.104 incr androgen
9.105 reduc luteinizing hormone

9.106 incr DHEA
9.107 incr Allopregnanolone
9.108 incr pregnenolone
9.2 Lipid dyshomeostasis
9.201 reduc cholesterol level
9.202 decr 24-hydroxycholesterol
9.203 decr 27-hydroxycholesterol
9.204 incr HDL
9.205 decr LDL
9.206 incr HMGCoAr
9.207 reduc chromosome mis-segregation
9.208 ameliorat hyperlipidemia
9.209 incr leptin
9.3 Growth factor restoration
9.301 incr NGF
9.302 incr VEGF
9.4 Metal homeostasis improvement
9.401 restor metal homeostasis
9.402 decr copper
9.403 inhib MAPK
9.5 Epigenetic modification
9.501 incr DNA methylation
9.502 amelior B6
9.503 amelior B12
9.504 amelior folate
9.511 inhib HDAC
9.512 incr histone acetylation
9.513 incr histone H3K9
9.521 incr miR-339-5p
9.522 decr miR-30a-5p
9.523 decr mir-206
9.524 decr miRNA-146a
9.6 Caspase inhibition
9.601 reduc caspase
9.602 reduc JNK
9.603 restor IGFBP3
9.7 Nitric oxide synthase modulation
9.701 reduc iNOS
9.8 Combinatorial improvements
9.801 activat multiple pathways
IMPROVE PERFORMANCE DEFICITS
10. Cognition/Memory/Learning
10.1 Cognition
10.101 improv cogniti

10.102 amelior cerebrovascular dysfunction
10.103 revers hypervascularity
10.104 incr CXCL1
10.105 improv MoCA
10.106 improv MMSE
10.107 reduc palmitoleic acid
10.108 incr DHA
10.109 incr c-fos
10.11 incr Egr-1
10.111 incr adiponectin
10.112 incr TPI
10.2 Memory
10.201 improv memory
10.202 incr B2R
10.203 incr B1R
10.204 incr GCSF
10.205 incr LTP
10.206 incr RLT
10.207 inhib Cdk5
10.208 inhib MAC
10.209 restor TrkB
10.21 restor melatonin
10.211 reduc CX3CR1
10.212 decr ATF4
10.213 incr dopamine
10.214 incr EphB2
10.3 Learning
10.301 improv learning
10.302 decr RORgammat
IMPROVE BEHAVIORAL DEFICITS
11. Behavioral problems
11.1 Behavior
11.101 improv behavior
11.2 Quality of Life
11.201 prevent nutritional deficien
11.201 improv quality of life
11.201 improv quality-of-life
11.202 allev menopausal
11.203 amelior dysphagia
11.204 restor IADL
11.205 allev ataxia
11.206 improv mobility
11.207 incr 25-OHD
11.208 reduc reduce stress

11.3 Agitation
11.301 reduc agitat
11.302 decr cortisol
11.4 Aggression
11.401 decr aggressi
11.5 Anxiety
11.501 reduc anxiety
11.6 Depression
11.601 reduc depression
11.7 Attention
11.701 improv attention
11.8 Apathy
11.801 reduc apathy
11.9 Sleep
11.901 improv sleep
11.902 reduc insomnia
REVERSE NEUROPATHOLOGY AND AD/DEMENTIA
12. Prevent and reverse neuropathology
12.1 Ameliorate neurodegeneration
12.101 reduc neuro degenerat
12.102 reduc astrogli
12.103 suppress activation microgli
12.104 attenuat NFAT
12.105 incr CNPase
12.106 incr Bcl-2
12.107 decr Bax
12.108 decr MDA
12.109 incr BDNF
12.11 incr neurotrophin
12.111 incr UCH-L1
12.112 inhibit PAI-1
12.113 rescu TGF-beta1
12.114 decr axonal dystrophy
12.115 incr PP2A
12.116 reduc LDH
12.117 incr PGRN
12.2 Attenuate neurotoxicity
12.201 alleviat neurotoxic
12.202 incr Ngb
12.3 Prevent apoptosis
12.301 inhib apopto
12.302 rescu dendritic spine
12.303 reduc Ephexin5
12.304 incr seladin-1

12.305 incr Hsp70
12.306 reduc TRPM2
12.307 reduc WT1
12.308 restor TERT
12.309 reduc p38MAPK
12.4 Protect neurons
12.401 protect neuron
12.402 enhanc autophagy
12.403 decr Beclin-1
12.404 decr SQSTM1
12.405 reduc synj1
12.406 incr CREB
12.407 decr IL-12p40/p70
12.5 Promote neurogenesis
12.501 incr neurogenesis
12.502 restor DCX
12.503 incr PCNA
12.504 incr 5-bromo-2'-deoxyuridine
12.505 incr heat shock transcription factor
12.506 incr Wnt3
PREVENT AND REVERSE AD/DEMENTIA
13. AD and Dementia
13.1 AD/Dementia
13.101 prevent AD
13.102 reduc prostaglandin
13.103 prevent dementia

(return to TOC)

APPENDIX 9 – PN/PAD BIOMARKERS AND SYMPTOMS

TABLE 7A-9a - Existing PN/PAD Biomarkers

# REC	BIOMARKER
2638	lesions
2536	inflammation
2320	toxicity
2277	nerve conduction velocity
2038	ankle brachial index
1549	blood pressure
1402	stenosis
1156	body mass index
1142	neurotoxic
1139	total cholesterol
1138	blood glucose levels
1091	degeneration
1061	hemoglobin A1c
932	blood flow
856	marker
841	proteins
748	atrophy
747	dorsal root ganglia
704	creatinine
700	oxygen
693	lipoprotein
671	growth factor
640	Schwann cell
616	demyelination
610	pain-free walking distance
549	C reactive protein
538	calcium
516	cytokine
499	triglycerides
495	low-density lipoprotein cholesterol
489	angiogenesis
455	axonal degeneration
435	Systolic blood pressure
426	circulation
425	high-density lipoprotein cholesterol
419	oxidative stress
413	plaque
412	occlusions
402	albumin level
399	glomerular filtration rate
391	ventricular ejection fraction
382	calcification
365	nerve damage
354	neurodegeneration
349	IgM
345	tumour necrosis factor-alpha
344	sodium
329	lipids
322	heart rate
318	edema
318	nitric oxide
309	apoptosis
308	fibrinogen
284	endothelial dysfunction
283	denervation
278	vascular endothelial growth factor
273	glycoprotein
266	IL-6
263	vitamin B(12) deficiency
262	stenoses
261	high homocysteine
251	angiotensin converting enzyme
247	amyloid
240	myelinated fibers
237	vibration perception threshold
222	weight loss
210	fatty acid
208	carotid artery intima-media thickness
206	nerve growth factor

202	T-cell
197	autoantibodies
195	thermal hyperalgesia
193	CD4
186	proinflammatory cytokine
185	insulin resistance
183	pulse wave velocity
175	diastolic blood pressure
170	nerve regeneration
168	platelet aggregation
162	glycated haemoglobin
159	lymphocytes
158	nerve fiber density
154	B-cell
152	Reactive oxygen species
151	arterial stiffness
147	capsaicin
147	lipid profile
135	platelet activation
128	IL-1beta
126	glutamate
126	Transthyretin
126	vitamin E deficiency
125	apolipoprotein
125	Vitamin D deficiency
123	acetylcholine
122	mechanical hyperalgesia
119	glutathione
118	compound muscle action potential
115	Mitochondrial dysfunction
115	nitric oxide synthase
115	white blood cell
114	creatine
110	waist circumference
108	creatinine clearance
107	lactate
106	von Willebrand factor
105	plasminogen activator inhibitor-1
104	pulse pressure
104	thrombin
103	urea

102	atherosclerotic plaque
102	IgA
101	vasculopathy
100	intercellular adhesion molecule-1
99	antioxidants
98	calcitonin gene-related peptide
96	uric acid
95	blood viscosity
94	Lipoprotein(a)
92	albumin excretion rate
92	substance P
84	fiber loss
84	malondialdehyde
81	Endothelial progenitor cells
81	orthostatic hypotension
80	fibrin
80	fibroblast growth factor
80	folic acid
78	transcutaneous oxygen pressure
74	creatine kinase
74	matrix metalloproteinase
74	thromboxane
73	thiamine
72	systemic sclerosis
70	IL-10
70	peak oxygen consumption
69	lipid peroxidation
69	prostacyclin
69	superoxide dismutase
69	troponin
68	D-dimer
66	mRNA levels
65	advanced glycation end product
65	magnesium
65	Zinc
64	anti-neutrophil cytoplasmic antibody
64	erythrocyte sedimentation rate

64	Red Blood Cell
61	monoclonal antibodies
61	oxygen saturation
61	P-selectin
60	heat shock
60	rheumatoid factor
59	acetylsalicylic acid
59	nitrogen
58	methionine
58	Neutrophils
55	Ca(2+)
55	Venous occlusion
54	glial fibrillary acidic protein
53	chemokines
53	Tissue Plasminogen Activator
52	Angiogenic growth factors
52	BDNF
52	hepatocyte growth factor
52	l-arginine
52	MetS
51	cardiac troponin T
51	epidermal growth factor
51	glucose metabolism
51	prothrombin
50	NF-kappaB
49	adenosine diphosphate
49	bone mineral density
49	cytochrome c
49	monocyte chemoattractant protein-1
49	protein kinases
48	bilirubin
48	thymidine
48	urinary albumin/creatinine ratio
47	glycosylation
45	neuronal damage
44	adiponectin
44	alanine
44	carbon dioxide
44	Mercury

43	erythrocytes
42	leucocytes
42	myelin basic protein
42	neuroinflammation
42	phosphorus
42	thromboangiitis
41	alkaline phosphatase
41	apolipoprotein B
41	CD34
41	free radicals
41	N-terminal pro-brain natriuretic peptide
41	transforming growth factor beta
40	arginine
40	DBP
40	dopamine
40	myeloperoxidase
40	sorbitol
39	apolipoprotein A-I
39	bacterial infection
39	cyclic AMP
39	endothelial damage
38	connexin 32
38	glycine
38	Noradrenaline
38	vitamin K
37	blood urea nitrogen
37	E-selectin
37	endothelin-1
37	matrix metalloproteinase 9
36	arachidonic acid
36	heme
36	IgG antibodies
36	niacin
35	glycogen
35	HCY
35	IL-8
35	interferon gamma
34	actin
34	catalase
34	cystatin C
34	histamine
34	Streptococcal

33	anti-ganglioside antibodies
33	catecholamine
33	cerebral ischemia
33	ferritin
33	glial activation
33	hypoperfusion
33	oxidative damage
32	anti-MAG antibodies
32	insulin levels
32	polyunsaturated fatty acids
31	parathyroid hormone
31	progesterone
30	beta 2 microglobulin
30	body fat
30	Gamma-aminobutyric acid
29	acetylcholinesterase
29	adenine
29	asymmetric dimethylarginine
29	Chlamydia pneumoniae
29	fibroblast growth factor 2
29	laminin
29	phospholipids
28	albumin/creatinine
28	brain atrophy
28	carotid-femoral pulse wave velocity
28	CD31
28	matrix metalloproteinase 2
28	Osteoprotegerin
28	phosphocreatine
28	Tau
28	thromboxane A2
27	antinuclear antibodies
27	Apolipoprotein E
27	cholinesterase
27	cyclooxygenase 2
27	epinephrine
27	GDNF
27	glutamine
27	high total cholesterol

27	methylmalonic acid
27	RAGE
27	vascular reactivity
26	Endothelin
26	glutathione peroxidase
26	growth hormone
26	HMG-CoA reductase
26	Hydrogen peroxide
26	leptin
26	miRNA
25	amyloid beta
25	cysteine
25	GP IIb/IIIa
25	Helicobacter pylori
25	Iron Deficiency
25	platelet-derived growth factor
25	sulfatide
24	aspartate aminotransferase
24	cadmium
24	IL-4
23	copper deficiency
23	immune activation
23	integrin
23	peroxynitrite
23	transferrin
22	CD8
22	lipase
22	Vitamin B1 deficiency
21	bradykinin
21	Escherichia coli
21	glutamic acid
21	methicillin-resistant Staphylococcus aureus
21	Oxidized low-density lipoprotein
21	prostate-specific antigen
20	acylcarnitine
20	adenosine triphosphate
20	aldosterone
20	arterial obstruction
20	CD40 ligand
20	folate deficiency

20	insulin-like growth factor I
20	thromboxane B2
20	transaminases
19	Ccl2
19	riboflavin
19	serum calcium
19	thrombomodulin
19	vascular calcifications
18	amyloid fibrils
18	c-Fos
18	caspase 3
18	docosahexaenoic acid
18	eicosapentaenoic acid
18	endothelial activation
18	estradiol
18	heme oxygenase 1
18	HIF-1alpha
18	luminal diameter
18	NADPH oxidases
18	renin
18	selenium
17	5-hydroxytryptamine
17	aortic pulse wave velocity
17	arterial compliance
17	bone density
17	compound motor action potential
17	CXCR4
17	cytomegalovirus infection
17	dehydration
17	desmin
17	elastin
17	excitotoxicity
17	High-mobility group box 1
17	IL-2
17	lactic acid
17	lead levels
17	porphobilinogen
17	prothrombin time
16	androgen
16	factor Xa

16	galanin
16	neoangiogenesis
16	PGE2
16	phytanic acid
16	proline
16	pyridoxal
15	activated partial thromboplastin time
15	calcium phosphate
15	calpain
15	cholestanol
15	cortisol
15	digoxin
15	DNA polymerase gamma
15	osteopontin
14	anti-GM1 antibody
14	antithrombin III
14	CD68
14	choline
14	CNTF
14	Fas
14	fos
14	MMA
14	myo-inositol
14	porphyrin
14	TBARS
13	atheromatous plaque
13	ceruloplasmin
13	complement levels
13	cyclic guanine monophosphate
13	E. coli
13	elastase
13	Fetuin-A
13	leucine
13	Lipoprotein-associated phospholipase A2
13	Neopterin
13	RNA levels
13	thyroxine
13	transglutaminase
13	vasopressin
12	adipokine
12	anticardiolipin antibodies
12	arterial calcifications

12	beta-carotene
12	C1q
12	calcineurin
12	caspases
12	Chondroitin sulfate
12	hydrogen sulfide
12	IgE
12	insulin deficiency
12	MEP
12	mitogen-activated protein kinases
12	NOx
12	PBMCs
12	Proteus
12	sE-selectin
12	spirochete
11	anti-gliadin antibodies
11	Coxsackie
11	dendritic cells
11	dipeptidyl peptidase
11	excitatory amino acids
11	fructose
11	gamma-glutamyltransferase
11	histidine
11	IL-12
11	Myelin breakdown
11	Pseudomonas aeruginosa
11	Resistin
10	ammonia
10	AMPA
10	apolipoprotein(a)
10	cathepsins
10	cotinine
10	Glutamate carboxypeptidase II
10	glycogen synthase
10	low birth weight
10	lysophosphatidic acid
10	Nrf2
10	polyglutamine
10	S-adenosylmethionine
10	threonine
10	tryptophan

9	adenosine monophosphate
9	alpha-synuclein
9	anticholinesterase
9	Aortic augmentation index
9	beta-galactosidase
9	BNP levels
9	BSA
9	CD133
9	cystathionine beta-synthase
9	deoxyuridine
9	enolase
9	fibrin D-dimer
9	fungi
9	heparan sulfate
9	iodine
9	low testosterone
9	phenylalanine
9	squalene
9	staphylococcal
9	vascular stiffness
8	arterial dilatation
8	Aspergillus
8	Butyrylcholinesterase
8	CBM
8	coagulation activation
8	corticosterone
8	glucagon
8	gonadotropin
8	inositol
8	isoprostane
8	leukotrienes
8	osteocalcin
8	paraoxonase-1
8	phosphates
8	Retroviruses
8	S100 beta
8	somatostatin
8	taurine
8	thyrotropin
7	4-hydroxy-2-nonenal
7	aldehyde dehydrogenase
7	amines

7	angiotensin II type 1
7	CD14
7	coronary calcification
7	HIV RNA levels
7	horseradish peroxidase
7	linoleic acid
7	monomethylarsonic acid
7	neuropilin-1
7	OX-42
7	phosphatidylinositol 3-kinase
7	thrombospondin
7	TNFR2
6	alcohols
6	arterial elasticity
6	citrulline
6	Cu
6	dimethylarsinic acid
6	factor XIII
6	fibroblast growth factor 23
6	FVII
6	glucuronic acid
6	GRP78
6	histone deacetylase 6
6	IL-18
6	kallikrein
6	lipid hydroperoxides
6	Methylglyoxal
6	N-acetylglucosamine
6	neurotoxic esterase
6	oxygen radicals
6	pentraxin
6	pERK
6	prolactin
6	quinolinic acid
6	Telomerase
6	transketolase
5	Acetylcarnitine
5	apolipoprotein A-II
5	apolipoprotein B-100
5	CD11c
5	CD16
5	CD86
5	cyclin D1

5	deoxyhemoglobin
5	dihydrotestosterone
5	galectin-3
5	Glyoxalase 1
5	guanosine monophosphate
5	Guanylate Cyclase
5	hyperphosphorylation
5	IL-13
5	inosine
5	L-selectin
5	lipofuscin
5	luteinizing hormone
5	monoamine oxidase
5	omega-3 index
5	perforin
5	phenyl valerate
5	platelet factor 4
5	pregnenolone
5	pristanic acid
5	retinol
5	sphingosine
5	thiocyanate
5	YKL-40
4	Adrenomedullin
4	amyloid precursor protein
4	angiogenin
4	angiotensinogen
4	apolipoprotein B-48
4	apolipoprotein C-III
4	arterial tonometry index (RHI)
4	beta-endorphin
4	chromogranin
4	dehydroepiandrosterone
4	dynactin
4	endopeptidases
4	erythrocyte aggregation
4	GHb
4	glutathione transferase
4	glycated albumin
4	homovanillic acid
4	hydroxymethylbilane synthase

4	IgG4-positive plasma cells
4	IL-17
4	IL-22
4	indole
4	Janus kinase 2
4	mannose
4	metallothionein
4	myostatin
4	nitrogen oxide
4	Nox2
4	S100A12
4	Sirtuin 1
4	SO2
4	soluble guanylyl cyclase
4	succinate dehydrogenase
4	tetrahydrobiopterin
4	tissue inhibitors of metalloproteinases
4	ubiquinone
4	valvular calcification
4	vasoactive intestinal peptide
3	acetaldehyde
3	acyl-CoA oxidase
3	Allograft inflammatory factor-1
3	arginase
3	B vitamin deficiency
3	brain iron accumulation
3	butyric acid
3	CFU
3	chorionic gonadotropin
3	connective tissue growth factor
3	CXCL10
3	eosinophil cationic protein
3	factor XII
3	Fusobacterium
3	glucagon-like peptide 1
3	Glucokinase
3	glutathione reductase
3	GTP cyclohydrolase
3	hemosiderin
3	hydroperoxide
3	hydroxyl radical antioxidant capacity
3	hyperoxia
3	iron deposition
3	kynurenine
3	LXR
3	m-calpain
3	mandelic acid
3	methemoglobin
3	mu-calpain
3	N-acetylaspartate
3	neurite loss
3	neurotensin
3	NF68
3	nicotinamide mononucleotide
3	Nociceptin
3	phosphatidylserine
3	PINK1
3	pipecolic acid
3	pregnancy-associated plasma protein-A
3	ryanodine
3	S-adenosylhomocysteine
3	sCD163
3	serum nitrate
3	sTWEAK
3	trimethylamine
3	waist-to-height ratio
3	xanthine oxidase
2	3-nitrotyrosine
2	32P
2	acid phosphatase
2	adenosine deaminase
2	adenosine kinase
2	adenylyl cyclases
2	agrin
2	aminolevulinic acid
2	aminopeptidases
2	apoB/apoA-I ratio
2	apolipoprotein A-IV
2	apolipoprotein AI-CIII-AIV gene cluster
2	aspartic acid

2	campesterol
2	carboxymethyl-lysine
2	Cardiometabolic index (CMI)
2	caspase 9
2	CCL4
2	Ceramide antibody levels
2	cyclin-dependent kinase 5
2	deoxyguanosine
2	deoxypyridinoline
2	docosapentaenoic acid
2	endostatin
2	estrone
2	follicle stimulating hormone
2	glutaredoxin
2	herpes simplex virus 1
2	hippuric acid
2	histone deacetylases
2	hydroxyproline
2	Janus kinase 1
2	JC virus
2	Ketones
2	kininase II
2	kininogen fractions
2	kynurenic acid
2	measles virus
2	midkine
2	miR-130a
2	miR-210
2	miR-27b
2	MuSK
2	omentin-1 level
2	phenylglyoxylic acid
2	polymorphonuclear neutrophils
2	Prevotella intermedia
2	protein tyrosine phosphatases
2	pyruvic acid
2	saturated fatty acid
2	suPAR level
2	tachykinins
2	transcription factor CHOP
2	TREM-1
2	vitamin C deficiency
2	Wnt5a
1	1,1-Diphenyl-2-picrylhydrazyl
1	1,7-dimethylxanthine
1	25-hydroxycholesterol
1	27-hydroxycholesterol
1	3,4-dihydroxyphenylacetic acid
1	3,4-dihydroxyphenylglycol
1	3,5,3'-triiodothyronine
1	4-pyridoxic acid
1	5-bromo-2'-deoxyuridine
1	7-ketocholesterol
1	8-hydroxyguanosine
1	8-oxoguanine
1	adenylate kinase
1	aniline hydroxylase
1	Anti-Mullerian hormone
1	antiphospholipids-induced
1	apolipoprotein D
1	Apolipoprotein L1
1	aryl hydrocarbon hydroxylases
1	bacterial endotoxins
1	benzo(a)pyrene
1	beta-mannosidase
1	calcium-dependent protein kinase
1	caspase 12
1	caspase 8
1	catechol-O-methyltransferase
1	CgA
1	complement C3b
1	complex II deficiency
1	complex IV deficiency
1	cyclic ADP-ribose
1	cyclooxygenase 1
1	cystathionine gamma-lyase

1	cysteinylglycine
1	dihydroxyphenylalanine
1	DL-alpha-tocopherol
1	elevated copper
1	Ferric iron
1	gamma-glutamylcysteine
1	gamma-tocopherol
1	glutaminase
1	glyceraldehyde
1	glyoxal
1	granzymes
1	hemopexin
1	hexokinase
1	High adiponectin
1	histone acetyltransferases
1	homocysteic acid
1	hypochlorite
1	isobutanol
1	keratins
1	L-ascorbic acid
1	lathosterol
1	NADH dehydrogenase

1	Nepsilon-(carboxymethyl)lysine
1	o-xylene
1	oncostatin
1	oxysterols
1	p-cresol
1	p300-CBP-associated factor
1	pancreatic polypeptide
1	Perlecan
1	Peroxiredoxins
1	phosphorylases
1	polyamines
1	polyQ
1	protoporphyrin IX
1	prulifloxacin
1	psychosine
1	pyrrole
1	pyruvate carboxylase
1	S-nitrosoglutathione
1	sex steroid hormones
1	ulifloxacin
	Urine kidney injury molecule-1

TABLE 7A-9b - Existing PN/PAD Symptoms/Diseases

# REC	SYMPTOM/DISEASE
17050	neuropathy
13577	peripheral neuropathy
9627	diabetes mellitus
9078	artery disease
8114	peripheral artery disease
6967	peripheral vascular disease
5942	pain
5016	ischemia
3095	hypertension
3014	cancer
2969	atherosclerosis
2861	neuropathic pain
2612	stroke
2152	diabetic peripheral neuropathy
2071	infection
2056	myocardial infarction
2051	cardiovascular disease
1983	intermittent claudication
1913	polyneuropathy
1796	coronary artery disease
1585	heart disease
1571	type 2 diabetes mellitus
1547	critical limb ischemia
1533	diabetic foot ulcer
1519	Disorder
1440	heart failure
1135	weakness
879	neutropenia
878	cerebrovascular disease
833	sensory neuropathy
832	retinopathy
799	coronary heart disease
779	allodynia
769	disability
769	obesity
747	renal failure
731	thrombosis
705	ataxia
675	abdominal aortic aneurysm
660	nephropathy
645	angina
645	renal disease

625	Congestive heart failure
623	multiple myeloma
621	peripheral artery occlusive disease
618	bleeding
618	hyperalgesia
613	chronic kidney disease
612	vasculitis
607	ischemic heart disease
602	restenosis
578	chronic obstructive pulmonary disease
578	fatigue
566	Charcot-Marie-Tooth disease
560	anemia
545	depression
521	thrombocytopenia
503	dyslipidemia
497	numbness
456	Hyperglycemia
455	nausea
444	sclerosis
441	hypersensitivity
433	atrial fibrillation
417	balance
412	chronic pain
400	mononeuropathy
391	lymphoma
389	rheumatoid arthritis
388	End stage renal disease
387	autonomic neuropathy
385	dementia
380	axonal neuropathy
379	mechanical allodynia
376	vomiting
373	gangrene
363	myopathy
362	palsy
360	hypercholesterolemia
358	diarrhea
354	ischemic stroke
352	Guillain-Barre syndrome
345	carpal tunnel syndrome
343	hyperlipidemia
332	leprosy
319	type 1 diabetes mellitus
314	hepatitis

308	renal insufficiency
306	encephalopathy
305	demyelinating peripheral neuropathy
304	motor neuropathy
303	Coronary Syndrome
295	neurological symptoms
285	neurologic disease
284	muscle weakness
280	Atherothrombosis
275	arrhythmia
273	inflammatory demyelinating polyneuropathy
271	metabolic syndrome
266	systemic lupus erythematosus
257	stiffness
254	amyloidosis
250	left ventricular hypertrophy
249	peripheral sensory neuropathy
249	radiculopathy
247	fractures
244	myelopathy
231	fibrosis
227	microalbuminuria
224	diabetic retinopathy
220	hypotension
213	multiple sclerosis
205	coronary disease
202	paresthesia
199	constipation
199	monoclonal gammopathy
190	proteinuria
187	diabetic nephropathy
187	Mixed Cryoglobulinemia
187	Sjogren's syndrome
179	nerve dysfunction
178	arterial hypertension
169	demyelinating polyradiculoneuropathy
169	sensorimotor polyneuropathy
165	Mononeuritis
162	angina pectoris
160	axonopathy
158	lung disease
157	Parkinson's disease
157	renal dysfunction
152	autoimmune disease
150	albuminuria

150	hypoxia
149	liver disease
149	sensorimotor neuropathy
147	hyperplasia
133	erectile dysfunction
126	renal impairment
125	artery calcification
124	vasculitic neuropathy
123	amyotrophic lateral sclerosis
123	systemic atherosclerosis
120	axonal polyneuropathy
119	hypothyroidism
119	myocardial ischemia
117	neurodegenerative disease
113	Alzheimer's disease
113	POEMS syndrome
110	atherosclerotic vascular disease
110	Osteoporosis
107	carotid artery disease
107	peripheral polyneuropathy
107	reactive hyperemia
103	neuromuscular disease
103	optic neuropathy
102	impaired glucose tolerance
101	endocrinopathy
101	Macrovascular disease
88	motor neuron disease
86	cerebral infarction
84	arterial stenosis
84	metastatic disease
80	atherogenesis
78	dysesthesia
77	macroglobulinemia
76	acquired immunodeficiency syndrome
75	Hyperhomocysteinemia
73	left ventricular dysfunction
73	peripheral atherosclerosis
72	complex regional pain syndrome
72	microvascular disease
70	dysphagia
70	polyarteritis nodosa
69	HIV disease
69	organ damage
68	granulomatosis
68	neuroarthropathy

67	eosinophilia
67	Restless legs syndrome
66	vascular calcification
65	hypoglycemic
65	polyangiitis
63	Churg-Strauss syndrome
61	amyloidotic polyneuropathy
61	neurodegenerative disorders
59	metabolic disease
58	impaired renal function
56	celiac disease
56	Crohn's disease
55	demyelinating disease
54	coronary atherosclerosis
54	inflammatory bowel disease
54	macroalbuminuria
53	sleep apnea
52	nephrotic syndrome
51	carotid atherosclerosis
48	gammopathies
47	connective tissue disease
47	proliferative retinopathy
46	cardiac autonomic neuropathy
43	Buerger's disease
43	Lyme disease
41	arteriosclerosis obliterans
41	polyvascular disease
41	vascular dysfunction
38	cutaneous vasculitis
37	Fabry disease
37	Miller Fisher syndrome
33	hypercoagulability
31	hypoalbuminemia
31	mitochondrial diseases
31	muscle ischemia
30	Castleman's disease
30	diplopia
30	Hansen's disease
29	Behcet's disease
29	chronic liver disease
28	sicca syndrome
26	hyperuricemia
25	gluten sensitivity
25	peripheral ischemia
21	Hypereosinophilic syndrome

20	aortic stiffness
18	coronary artery stenosis
17	normoalbuminuria
16	kidney dysfunction
15	CLTI
14	dysmetria
12	malaria
12	mechanical stress
12	rheumatoid vasculitis
11	hypomagnesemia
11	neurone disease
10	neurosyphilis
10	social isolation
9	low physical activity
8	bulbar palsy
8	Hyperfibrinogenemia
6	hypercapnia
6	Wolfram

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